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CADTH COMMON DRUG REVIEW

Clinical Review Report

SEBELIPASE ALFA (KANUMA)

(Alexion Pharmaceuticals, Inc.)

Indication: Indicated for the treatment of infants, children, and adults diagnosed with lysosomal acid lipase (LAL) deficiency

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Abbreviations

AE	adverse event
ADA	anti-drug antibodies
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDR	CADTH Common Drug Review
CI	confidence interval
CESD	cholesteryl ester storage disease
CLDQ	Chronic Liver Disease Questionnaire
CLF	Canadian Liver Foundation
CSR	clinical study report
DB	double blind
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FACT	Functional Assessment of Cancer Therapy
FAS	full analysis set
HDL-C	high-density lipoprotein cholesterol
HFA	height for age
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IAR	infusion-associated reaction
IV	intravenous
LAL	lysosomal acid lipase
LDL-C	low-density lipoprotein cholesterol
LFA	length-for-age
LLM	lipid-lowering medications
MCID	minimal clinically important difference
OL	open-label
PedsQL	Pediatric Quality of Life Inventory
PES	primary efficacy analysis set
PP	per-protocol
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SF-36	Medical Outcomes Study Short Form (36) Health Survey
SFA	stature-for-age
TEAE	treatment-emergent adverse event
TG	triglyceride

ULN	upper limit of normal
WDAE	withdrawal due to adverse event
WFA	weight-for-age
WFH	weight-for-height
WFL	weight-for-length
WHO	World Health Organization

Drug	Sebelipase alfa (Kanuma)
Indication	Indicated for the treatment of infants, children, and adults diagnosed with lysosomal acid lipase (LAL) deficiency.
Reimbursement Request	For long-term enzyme replacement therapy in patients with LAL deficiency.
Dosage Form(s)	Solution for infusion 2 mg/mL concentrate 20 mg/10 mL (2 mg/mL) solution in single-use vials
NOC Date	December 15, 2017
Manufacturer	Alexion Pharmaceuticals, Inc.

Executive Summary

Introduction

Lysosomal acid lipase (LAL) deficiency is a rare, life-threatening, progressive multi-systemic disease associated with early mortality and significant morbidity. It is caused by genetic mutations that lead to a total loss, or a marked decrease, in LAL enzyme activity, and can affect people of all ages.[1-3] The reduction or absence of LAL results in disruption of lipid metabolism, with a buildup of cholesteryl esters and triglycerides in vital organs, particularly the liver, gut, adrenals, and blood vessels.[1-3] In the past, LAL deficiency presenting in infants was known as Wolman disease, and LAL deficiency presenting in children and adults was known as cholesteryl ester storage disease (CESD). Infants diagnosed with LAL deficiency have a mortality rate of nearly 100% by 12 months of age, with the median age of death of 3.7 months.[1,2] The estimated prevalence in its early-onset form is 1 per 350,000 births.[4] The prevalence of late-onset LAL deficiency ranges from 8 to 25 per million, depending on geographical location and ethnicity.[5]

Sebelipase alfa has a Notice of Compliance with conditions from Health Canada (pending the results of trials to verify its clinical benefit) for the treatment of infants, children, and adults diagnosed with LAL deficiency.[6] The Health Canada–recommended starting dose in infants (less than six months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous (IV) infusion once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly (and possibly 5 mg/kg weekly) may be considered.[6] The Health Canada–recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to six months of age is 1 mg/kg administered as an IV infusion once every other week.[6]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of sebelipase alfa for the treatment of infants, children, and adults diagnosed with LAL deficiency.

Results and Interpretation

Included Studies

Two trials, ARISE and VITAL, met the inclusion criteria for this review. The VITAL trial (N = 9) was a phase II/III, multi-centre, open-label, single-arm study of sebelipase alfa in patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to six months of age. The age range at study entry was 1 month to 6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Based on clinical response, dose escalation to 3 mg/kg once weekly could be considered after receiving at least four infusions at a dose of 1 mg/kg once weekly. A further dose escalation to 5 mg/kg once weekly was allowed. In the VITAL trial, the primary efficacy end point was the proportion of patients surviving to 12 months of age.

The ARISE trial (N = 66) was a phase III, randomized, multi-centre, double-blind, placebo-controlled study of children and adults with LAL deficiency. Patients were randomized to receive sebelipase alfa at a dose of 1 mg/kg (n = 36) or placebo (n = 30) once every other week for 20 weeks in the double-blind period. Randomization was stratified by: age at randomization (< 12 years versus ≥ 12 years); average screening alanine aminotransferase (ALT) level (< 3 times the upper limit of normal [ULN] versus ≥ 3 times ULN); and use of lipid-lowering medications (LLM) (yes, no). The age range at randomization was 4 years to 58 years old. The ARISE trial evaluated improvements in multiple disease-related abnormalities in children and adults. In the ARISE trial, the primary efficacy outcome measure was the proportion of patients who achieved ALT normalization (i.e., ALT below the age- and gender-specific ULN provided by the central laboratory performing the assay) at the end of the double-blind period (week 20).

Key limitations in both trials were the small sample size and the lack of long-term follow-up. In addition, in the ARISE trial surrogate outcomes were used instead of hard clinical outcomes, and in the VITAL trial a historical control for the primary outcome was used.

Efficacy

There were no deaths during the double-blind period of the ARISE trial, however the double-blind period was short (20 weeks) and there is no evidence to address long-term and key clinical end points such as the need for liver transplant, cardiovascular events, and death. In the VITAL trial, the percentage of patients in the primary efficacy analysis set surviving to 12 months of age was 67% (6 of 9 patients), with an exact 95% confidence interval (CI) for survival of 29.9% to 92.5%. As of May 2017, five patients had survived beyond four years of age and were continuing to receive sebelipase alfa. The median age (range) at last exposure in the study was 4 years and 7 months (4 years and 2 months to 6 years and 5 months). The median follow-up time in the study was 4 years and 1 month.

All five surviving patients were living at home and were reported by the manufacturer to be making normal social and developmental progress. [redacted] In the historical control cohort — a multi-centre, multinational, retrospective natural history study, which included 21 untreated infants with LAL deficiency and early growth failure, with median (range) age at diagnosis of 2.5 months (1.0 month to 5.0 months) — none of the patients survived beyond 8 months of

age, and the percentage (exact 95% CI) of patients surviving to 12 months of age, determined using the same methodology as in the VITAL trial, was 0% [redacted].[8,9]

From the patient group input received by the CADTH Common Drug Review (CDR) on this submission, it is clear that patients consider improved quality of life and reduction in pain to be important outcomes of treatment. The VITAL trial did not assess health-related quality of life (HRQoL) or other patient-reported outcomes. The ARISE trial assessed HRQoL using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Chronic Liver Disease Questionnaire (CLDQ), and Pediatric Quality of Life Inventory (PedsQL). [redacted]

In the VITAL trial, growth deceleration from birth was observed for all eight patients with available weight data. Improvements in growth were observed for all six surviving patients. Weight-for-age (WFA) percentile, a key parameter of growth evaluation in infants, improved significantly for all patients from baseline through the last assessment prior to data cut-off for the clinical study report (CSR) provided by the manufacturer (June 10, 2014). Data for other growth parameters such as length-for-age (LFA) supported the trends observed for WFA. [redacted]

In both trials, sebelipase alfa reduced lipid levels, liver enzymes, and liver fat content (assessed in the ARISE trial only); however, it is unclear how these surrogate outcomes related to key clinical outcomes on long-term survival. In particular, it is uncertain to what degree sebelipase alfa may delay (or stop) progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, cardiovascular events, or death. While the VITAL trial had treatment for up to four years, this is only a fraction of the expected lifelong treatment patients in clinical practice would receive. Hence, the long-term safety and efficacy profile of sebelipase alfa beyond four years is uncertain.

In the open-label (OL) extension period of the ARISE trial, it appeared that ALT and aspartate aminotransferase (AST) normalization were sustained at week 36, along with continual improvements in LDL-C, HDL-C, non-HDL-C, and triglycerides (TG); however, the numbers of patients contributing to these outcomes were small, and due to the limitations inherent to the ARISE extension period (open-label nature of the study, the lack of a proper control group, and the lack of power necessary to perform meaningful statistics), no definitive conclusions can be made regarding the long-term treatment effect of sebelipase alfa 1mg/kg.

Harms

In the VITAL trial, three patients have died due to complications related to disease progression (hepatic failure or cardiac arrest) or a non-study-related procedure (peritoneal hemorrhage following abdominal paracentesis). These patients died after receiving

between one and four infusions of sebelipase alfa. Treatment-emergent adverse events have been reported for all nine (100%) patients. The most frequently reported treatment-emergent adverse events (TEAEs) were vomiting, diarrhea, pyrexia, rhinitis, anemia, cough, catheter-site infection, device-related infection, dermatitis diaper, nasopharyngitis, urticaria, tachycardia, rash, chills, and decreased appetite. One patient experienced four study drug-related serious adverse events (SAEs), which were characterized as infusion-associated reactions (IARs). Anaphylaxis was not reported in any patient treated with sebelipase alfa in this study. IARs have been reported for four patients, most commonly pyrexia, vomiting, tachycardia, and chills, and have been predominantly mild and non-serious. No patient has discontinued treatment due to IARs or other study drug-related TEAEs, and no patient has had a permanent dose reduction due to poor tolerability. One patient was discontinued from treatment following a non-study drug-related TEAE of bradycardia, and died of hepatic failure prior to the next scheduled infusion. Four patients have had a dose modification (interruption or decrease) during one or more study infusions due to a TEAE. There is evidence of anti-drug antibodies (ADA) formation in four of the seven patients who have been tested. ADA positivity was confirmed as early as weeks 5 and 8 (3 patients), and the fourth patient became positive at week 59. Three patients have persistent ADA positivity (> 1 assessment).

In the ARISE trial, there were no deaths. The incidence of SAEs in the double-blind period of the study was low (two patients in the sebelipase alfa group and one patient in the placebo group).The percentage of patients treated with sebelipase alfa who experienced TEAEs was 86% versus 93% of those who received placebo. Overall, the most common (i.e., incidence > 10%) TEAEs reported among the 36 patients in the sebelipase alfa group were headache (28%), pyrexia (19%), diarrhea, oropharyngeal pain, and upper respiratory tract infection (each 17%), and epistaxis and nasopharyngitis (each 11%). During the double-blind period, two (6%) of 36 patients in the sebelipase alfa group experienced a total of 10 IARs, and four (13%) of 30 patients in the placebo group experienced a total of five IARs. Anaphylaxis was not reported in any patient treated with sebelipase alfa in this study. A total of 14.3% of patients in the sebelipase alfa group had at least one positive ADA test during the double-blind period. In the OL extension period of the ARISE trial no new safety signals were apparent, with 96% of patients experiencing at least one adverse event (the most common of which were headache, diarrhea, and pyrexia), and 6% experiencing a SAEs. In addition, five patients (14%) were positive for antibodies in the extension analysis set. However, due to the limitations inherent to the ARISE extension period (open-label nature of the study, and the lack of a proper control group), no definitive conclusions can be made regarding the long-term treatment safety of sebelipase alfa 1mg/kg.

Potential Place in Therapy[1]

There are two distinct clinical presentations of LAL deficiency: the rapidly progressing infant-onset type (previously Wolman disease) and the later onset type in children and adults (previously CESD). Both types are associated with hepatic and extrahepatic morbidity and mortality.

The rapidly progressive type of LAL deficiency that presents in infancy (i.e., the sebelipase alfa VITAL trial population) is associated with complete loss of LAL enzyme function caused by mutations in the LIPA gene, resulting in 100% mortality before one year of age. Diagnosis of this type of LAL deficiency in Canada is typically made within the first two to

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

six months of life, based on clinical (e.g., early growth restriction), biochemical, LAL enzyme activity assays, and LIPA gene analysis. It is at the moment not part of newborn screening programs.

The other form of LAL deficiency in children and adults (i.e., the sebelipase alfa ARISE trial population) has a poorly defined clinical course because of substantial variability in clinical phenotype characterized by a much wider variation in LAL enzyme activity, as compared with the infant form, in that enzyme activity may range from being decreased to completely absent. Age of presentation may be as late as the sixth decade of life. Consequently, this form is more difficult to diagnose and these patients likely are underdiagnosed in Canada, and elsewhere. In addition to clinical, biochemical, and enzyme activity assessments, diagnosis also typically requires liver biopsy (evidence of microvesicular steatosis and cirrhosis), and sophisticated histological and immunohistochemical analyses to help differentiate from non-alcoholic fatty liver disease. The key clinical concerns in this subpopulation are liver cell failure progressing to cirrhosis, and hyperlipidemia and resultant risk of early atherosclerotic cardiovascular disease and/or stoke, and premature death.

The clinical expert consulted by CADTH noted that there is an unmet need for an effective and safe treatment that alters the natural history of LAL deficiency. Prior to sebelipase alfa, treatment for both types of LAL deficiency was limited to LLMs, hematopoietic stem cell transplantation and bone marrow transplantation, and liver transplantation. However, there is limited or no evidence that these treatments delay progression or modify the risk of death in a significant way in patients with LAL deficiency. As well, these treatments may be associated with increased morbidity and mortality. For example, hematopoietic stem cell transplantation and bone marrow transplantation are not used routinely for either group of LAL deficiency patients because of high mortality rates (> 70%).

Based on the data reviewed from the VITAL trial, sebelipase alfa appears to impact mortality in the infantile-onset form of LAL deficiency. These patients should be initiated with treatment after diagnosis is established by clinical, biochemical, LIPA gene analysis, and lysosomal activity assays. Monitoring of treatment and outcomes will be necessary and should be done at centres with access to specialists in the care of patients with LAL deficiency, including a multidisciplinary team of providers in pediatric cardiology, gastroenterology, surgery, genetics, pathology, nutrition, and development follow-up.

The design and duration of the ARISE trial, particularly the focus on surrogate outcomes as opposed to key clinical end points (need for liver transplant, atherosclerotic cardiovascular disease, and death), as well as the heterogeneity of the disease and progression of the late-onset form, make it difficult to decide in which patients sebelipase alfa may be of benefit, and what is the optimal dose for the individual patient. LAL enzyme assays of significantly decreased LAL activity, progression of liver disease as assessed by hepatomegaly, liver biopsy, and growth failure in children, are factors that may be considered by clinicians in considering sebelipase alfa use. There is a need for greater clarity regarding time of initiation, and need for continued gathering of data for understanding the translation of improvements in surrogate markers to relevant long-term end points. If treated with sebelipase alfa, children and adults would also require close management from a multidisciplinary care team with experience managing these patients.

Conclusions

Two trials, ARISE and VITAL, met the inclusion criteria for this review. While sebelipase alfa seems to improve growth, biochemical markers, and survival in patients presenting with LAL deficiency in infancy in the VITAL trial, with 67% of sebelipase alfa-treated patients surviving to 12 months of age, there is uncertainty regarding the long-term efficacy of sebelipase alfa in continuing to improve survival for infants who survived to 12 months. In the ARISE trial, sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in some children and adults with LAL deficiency. However, it is uncertain if sebelipase alfa delayed or stopped important LAL deficiency-related morbidities, including progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, or cardiovascular events in the non-infant population. Survival could not be evaluated in ARISE. Also, there was no improvement in HRQoL as compared with placebo. The safety profile of sebelipase alfa was similar to placebo in the controlled phase of the trials except for ADA formation. While there were no apparent differences in safety results for sebelipase alfa between the controlled phase of the studies and the open-label extension, conclusions regarding the long-term safety of sebelipase alfa in patients with LAL deficiency are limited, due to the absence of a comparator arm and the short duration of treatment.

Table 1: Summary of Results

Outcome	ARISE		VITAL
	Sebelipase Alfa	Placebo	Sebelipase Alfa
Survival			
Per cent surviving during the 20-week double-blind period in the ARISE trial	100%	100%	NA
Per cent surviving to 12 months of age (95% CI)[a]	NA	NA	67 (29.93 to 92.51)
Per cent surviving to 18 months of age (95% CI)[a]	NA	NA	[redacted]
Per cent surviving to 24 months of age (95% CI)[a]	NA	NA	[redacted]
Per cent surviving to 30 months of age (95% CI)[a]	NA	NA	[redacted]
Per cent surviving to 36 months of age (95% CI)[a]	NA	NA	[redacted]
FACIT-F total score – full analysis set at last DB measurement[b]			
n	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
Median (range)	[redacted]	[redacted]	
Difference	[redacted]		
P value[b]	[redacted]		
CLDQ total score – full analysis set at last DB measurement[d]			
n	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
Median (range)	[redacted]	[redacted]	
Difference	[redacted]		
P value[b]	[redacted]		
PedsQL total score – full analysis set at last DB measurement[e]			
n	[redacted]	[redacted]	
Mean (SD)	[redacted]	[redacted]	
Median (range)	[redacted]	[redacted]	
Difference	[redacted]		
P value[b]	[redacted]		
Patients with > 0 AEs			
n (%)	31 (86)	28 (93)	9 (100)
SAEs			
n (%)	2 (6)	1 (3)	8 (89)
WDAEs			
n (%)	1 (3)	0	0
Number of deaths			
n (%)	0	0	3 (33)
Notable harms, n (%)			
Infusion-associated reactions	2 (6)	4 (13)	4 (44)
Anaphylaxis	0	0	0

Outcome	ARISE		VITAL
	Sebelipase Alfa	Placebo	Sebelipase Alfa
ADA positive	5/35 (14)	0	4/7 (57)
Chest discomfort	1 (3)	0	0
Tachycardia	0	0	2 (22)
Headache	10 (28)	6 (20)	0
Anxiety	2 (6)	0	0

ADA = anti-drug antibodies; AE = adverse event; CI = confidence interval; CLDQ = Chronic Liver Disease Questionnaire; DB = double blind; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; NA = not applicable; OR = odds ratio; PedsQL = Pediatric Quality of Life Inventory; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Exact CI calculated using Clopper-Pearson method.

[b] FACIT-F total score only available for patients who were 17 years or older at date of informed consent. The total score ranges from 0 to 52; a higher value indicates a better quality of life.

[c] Wilcoxon rank sum test for treatment differences.

[d] CLDQ questionnaire only available for patients who were 17 years or older at date of informed consent. Total score range from 0 to 7; higher values indicate a better quality of life.

[e] PedsQL questionnaire only available for patients who were 5 years to ≤ 18 years old at date of informed consent. Total score range from 0 to 100; higher values indicate a better quality of life.

Introduction

Disease Prevalence and Incidence

Lysosomal acid lipase (LAL) deficiency is a rare, life-threatening, progressive multi-system disease associated with early mortality and significant morbidity. It is caused by genetic mutations that lead to a total loss, or a marked decrease, in LAL enzyme activity, and can affect people of all ages.[1-3] The reduction or absence of LAL results in disruption of lipid metabolism, with a buildup of cholesteryl esters and triglycerides in vital organs, particularly the liver, gut, adrenals, and blood vessels. [1-3] In the past, LAL deficiency presenting in infants was known as Wolman disease, and LAL deficiency presenting in children and adults was known as cholesteryl ester storage disease (CESD).

Infants diagnosed with LAL deficiency have a mortality rate of nearly 100% by 12 months of age, with the median age of death of 3.7 months.[1,2] Common clinical features of LAL deficiency in infants are malabsorption (due to diarrhea and vomiting), growth retardation, as well as severe hepatic disease, as evidenced by massive hepatomegaly, elevation of transaminases, hyperbilirubinemia, coagulopathy, and hypoalbuminemia.[10,11] Disease presentation in children and adults has a more variable clinical course because of greater variability in LAL enzyme activity in these patients, and hence less severe illness as compared with those with the infant-onset form.[12] These patients typically have elevated serum transaminases, hepatomegaly, and dyslipidemia (elevated triglycerides [TG] and low-density lipoprotein cholesterol [LDL-C] levels, and reduced high-density lipoprotein cholesterol [HDL-C] levels), placing them at increased risk of developing cardiovascular disorders, liver cirrhosis, or complications of liver cirrhosis and premature death.[12]

As is the case with many rare diseases, published information about the incidence and prevalence of LAL deficiency is limited. The estimated prevalence in its early-onset form is one case per 350,000 births.[4] The prevalence of late-onset LAL deficiency ranges from eight to 25 cases per million, depending on geographical location and ethnicity, where the estimated prevalence of the disease in the German population is 25 cases per million, while the estimated prevalence of late-onset LAL deficiency in North America is eight cases per million in Caucasian and Hispanic populations.[5] However, the prevalence data may be inaccurate and underestimated, due to the nonspecific signs and symptoms, which can lead to underdiagnosis and misdiagnosis.[4,13] LAL deficiency can be diagnosed through both physical findings (abdominal distention with hepatosplenomegaly) and by confirmation of absent or markedly reduced LAL enzyme activity in peripheral blood leukocytes, fibroblasts, or dried blood spots.[11,14]. LAL deficiency is not included in newborn screening in Canada.

Standards of Therapy

Sebelipase alfa is the only treatment approved for LAL deficiency. The standard of care has been therapies such as lipid-lowering medications (LLMs), hematopoietic stem cell transplantation (HSCT) for infants, and liver transplantation, to mitigate some symptoms and clinical manifestations of the disease.[1,2] However, these are only supportive and do not address the underlying pathology of the disease, which is the lack or decrease of LAL enzyme activity. Given that these options do not address the underlying etiology of the disease, they have not been shown to modify clinical outcomes in patients with LAL deficiency.

Statins and other LLMs have been prescribed to normalize elevated serum lipid levels, but dyslipidemia persists and worsens with disease progression.[1] Also, LLMs do not prevent liver or extrahepatic complications. HSCT has been used for LAL deficiency in infants with little success. Fatal toxicity, sustained engraftment challenges, and a lack of timely differentiation and expression of donor cells in target tissues are unresolved causes of high HSCT failure for LAL deficiency.[2] In addition, the rapidly progressive nature of infantile LAL deficiency, the poor condition of infants at the time of diagnosis, and the requirement for chemo-ablative pre-conditioning in preparation for HSCT, which most infants with LAL deficiency are unable to survive, are other reasons for the limited effect of HSCT.[15] Liver transplantation has only been attempted in a handful of patients with LAL deficiency. Due to this limited evidence base, no conclusions about the efficacy of this intervention can be drawn.[4] Additionally, according to the clinical expert consulted for this review, liver transplant may delay morbidity and possibly mortality in some patients, but because the underlying cause of LAL deficiency has not been treated, the transplanted liver is still susceptible to damage from excess lipid levels and extrahepatic manifestations still occur.

Drug

Sebelipase alfa is a recombinant human LAL that binds to cell surface receptors and is subsequently internalized into lysosomes. It catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids.[6]

Sebelipase alfa has a Notice of Compliance with conditions from Health Canada (pending the results of trials to verify its clinical benefit) for the treatment of infants, children, and adults diagnosed with LAL deficiency.[6] The Health Canada–recommended starting dose in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency is 1 mg/kg administered as an intravenous (IV) infusion once weekly, which may be increased to 3 mg/kg once weekly based on clinical response. The product monograph indicates that, in one infant who exhibited suboptimal growth response, doses were escalated to 5 mg/kg weekly.[6] The Health Canada–recommended dose in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age is 1 mg/kg administered as an IV infusion once every other week.[6] Sebelipase alfa is available as an aqueous concentrate for solution for infusion in single-use vials for IV use. Each vial contains 20 mg of sebelipase alfa in 10 mL.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of sebelipase alfa for the treatment of infants, children, and adults diagnosed with LAL deficiency.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Patients with LAL deficiency Subpopulations: • age (infants < 1 year of age, children aged 1 year to < 18 years, and adults) • genetic mutation category • presence of cirrhosis
Intervention	Sebelipase alfa 1 mg/kg administered as an IV infusion once weekly in infants (< 6 months of age) presenting with rapidly progressive LAL deficiency. Dose escalation to 3 mg/kg to 5 mg/kg once weekly based on clinical response. Sebelipase alfa 1 mg/kg administered as an intravenous infusion once every other week in children and adults who do not present with rapidly progressive LAL deficiency prior to 6 months of age.
Comparators	Placebo
Outcomes	**Key efficacy outcomes:** • Survival • HRQoL (for patients and carers)[a] • Patient-reported symptoms (improvement in pain measured by any valid method, improvement in gastrointestinal symptoms)[a] • Cardiovascular events[a] • Liver transplant[a] • Change in weight and length **Other efficacy outcomes:** • Cholesterol level (total, LDL and HDL) • Triglycerides level • Transaminase level • Liver fat content **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms/harms of special interest (infusion reactions, hypersensitivity reaction, immunogenicity, ADA formation, chest discomfort, tachycardia, headache, anxiety, anemia)
Study Design	Published and unpublished phase III RCTs

ADA = anti-drug antibodies; AE = adverse event; HDL = high-density lipoprotein; IV = intravenous; LAL = lysosomal acid lipase; LDL = low-density lipoprotein; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Outcomes identified as important, based on patient input.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Kanuma (sebelipase alfa) and lysosomal acid lipase deficiency.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 27, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 11, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Clinical trials; and Databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in the Included Studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

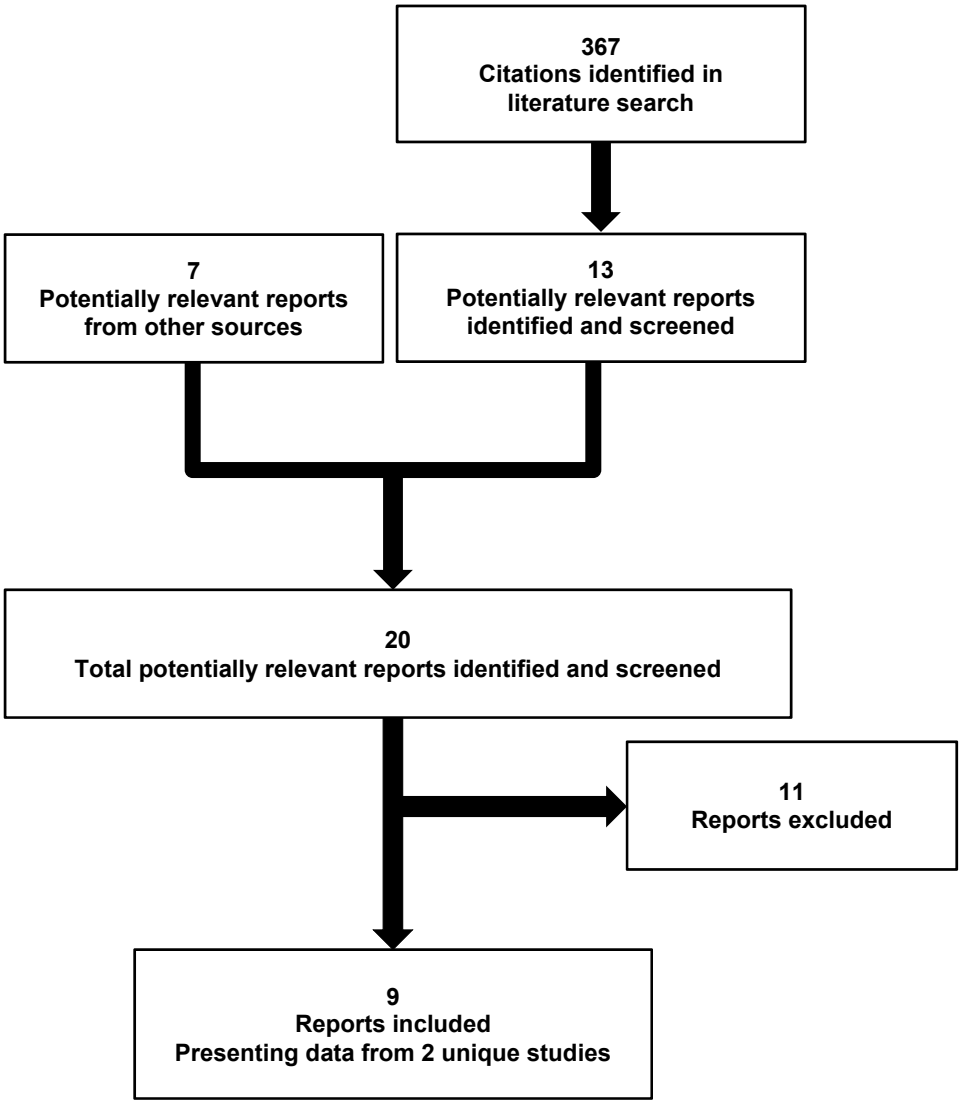

Table 3: Details of Included Studies

		ARISE	VITAL
Designs & Populations	**Study Design**	DB placebo-controlled, phase III RCT	OL, single-arm, phase II/III trial
	Locations	55 study centres in 17 countries including Australia; Europe (Croatia, Czech Republic, France, Germany, Greece, Italy, Poland, Russia, Spain, UK); Middle East (Turkey); North America (US and Canada); and South America (Argentina), Japan, Mexico	9 centres in the UK, US, France, Turkey, Saudi Arabia, Taiwan, Italy, and Egypt
	Randomized (N)	66	9
	Inclusion Criteria	• At least 4 years of age on the date of informed consent • Deficiency of LAL enzyme activity confirmed by dried blood spot testing at screening • Had ALT ≥ 1.5 × the ULN on 2 consecutive screenings[a] • Patients who were taking LLM had to have been taking a stable dose for at least 6 weeks prior to randomization and had to continue taking a stable dose for at least the first 32 weeks of treatment in the study	Male or female child with a documented decreased LAL activity relative to the normal range of the lab performing the assay or documented result of molecular genetic testing (2 mutations) confirming a diagnosis of LAL deficiency. Growth failure with onset before 6 months of age[c]
	Exclusion Criteria	• Severe hepatic dysfunction (Child-Pugh Class C) • Had undergone a previous hematopoietic or liver transplant procedure • Known causes of active liver disease other than LAL deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excess alcohol consumption) • HIV • Poorly-controlled diabetes • Cancers other than non-melanoma skin cancer • Known hypersensitivity to eggs	• Myeloablative preparation, or other systemic pre-transplant conditioning, for hematopoietic stem cell or liver transplantation • Previous hematopoietic stem cell or liver transplant • Clinically important concurrent disease or comorbidities [redacted] • [redacted] • Patients who were older than 24 months of age[d] • Known hypersensitivity to eggs

		ARISE	VITAL
Drugs	**Intervention**	1 mg/kg intravenous infusion of sebelipase alfa every other week	Treatment initiated at a starting dose of 0.35 mg/kg IV infusion of sebelipase alfa once weekly. The dose was escalated to 1 mg/kg once weekly once acceptable safety and tolerability had been demonstrated during at least 2 infusions at the dose of 0.35 mg/kg. All patients exhibiting a suboptimal response[e] to treatment based on protocol-defined criteria could be considered for further dose increase to 3 mg/kg once weekly. Patients receiving long-term treatment on a stable once-weekly dose could be switched to every other week dosing schedule at the same total dose (mg/kg) per infusion.[f] Dose reductions were also permitted in the event of poor tolerability. An option for dose escalation to 5 mg/kg once weekly in patients who had evidence for a continued suboptimal response / loss of efficacy in association with the presence of neutralizing antibodies.[g]
	Comparator(s)	Matched placebo	Survival at age 12 months in the historical control group (n = 21) of 0% (95% CI, 0% to 16.1%)
Duration	**Phase**		
	Screening period	6 weeks	[redacted]
	Double-blind	20 weeks	NA
	Open-label		Up to 4 years
	Open-label extension period	Up to 130 weeks	NA
	Follow-up	Phone call at least 4 weeks after the last dose of study drug	[redacted]
Outcomes	**Primary End Point**	The proportion of patients who achieved ALT normalization at the end of the DB period (week 20)[b]	The proportion of patients surviving to 12 months of age
	Other End Points	• FACIT-F • CLDQ • PedsQL Generic Core Scales • Relative reduction in LDL-C • Relative reduction in non-HDL-C • Relative increase in HDL-C • Relative reduction in TG • Proportion of patients with an abnormal baseline AST (i.e., > ULN) who achieved normalization of AST • Relative reduction in liver fat content (in the subset of patients for whom this assessment was performed) • Safety	• Proportion of patients surviving at 18 and 24 months of age • Median age at death • Changes from baseline in percentiles and/or z scores as determined from WHO criteria for WFA and WFL • Changes from baseline in ALT • Changes from baseline in AST • Safety

		ARISE	VITAL
NOTES	**Publications**	Burton et al.[16]	Jones et al.[17]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CLDQ = Chronic Liver Disease Questionnaire; DB = double-blind; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue scale; HDL-C = high-density lipoprotein cholesterol; HFA = height for age; IV = intravenous; LAL = lysosomal acid lipase; LDL-C = low-density lipoprotein cholesterol; LFA = length-for-age; LLM = lipid-lowering medications; NA = not available; OL = open-label; PedsQL = Pediatric Quality of Life Inventory; RCT = randomized controlled trial; TG = triglycerides; ULN = upper limit of normal; WFA = weight-for-age; WFL = weight-for-length; WHO = World Health Organization; wt = weight; x = times.

Note: Five additional reports were included: CDR submission;[7] FDA statistical review(s) and medical review(s) for Kanuma (sebelipase alfa);[18,19] NICE Sebelipase Alfa for Treating Lysosomal Acid Lipase Deficiency Committee papers;[20] and the European Medicines Agency (EMA) report.[21]

[a] The ULN for ALT for the central laboratory was dependent on age and gender; the ULN for the central laboratory was 34 U/L for females 4 to 69 years and males 1 to 10 years and 43 U/L for males aged 10 to 69 years.

[b] Defined as ALT below the age- and gender-specific ULN provided by the central laboratory performing the assay.

[c] Growth failure was defined by wt decreasing across at least two of the 11 major centiles on a standard WHO WFA chart (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th); or body wt in kg below the 10th centile on a standard WHO WFA chart AND no wt gain for the two weeks before screening; or loss of > 5% of birth wt in a child who is older than two weeks of age. In the unusual circumstance where a patient had a rapidly progressive course of LAL deficiency but did not meet the growth failure criteria as defined above, the patient could be enrolled in the study if the Investigator had substantial clinical concerns based on evidence of rapid disease progression that required urgent medical intervention. Inclusion under these exceptional circumstances required submission of a written summary of the patient's medical status for review by the manufacturer, and this summary had to be approved by a written confirmation from the manufacturer after consultation with the study Safety Committee. The patient had to meet all other entry criteria as stated.

[d] Patients older than eight months of age on the date of first infusion were not eligible for the primary efficacy analysis.

[e] Within a patient's first three months of treatment, suboptimal response was defined as meeting at least two of the following criteria: failure to gain an average of 5 g/kg body wt per day, and the presence of any of the following (WHO WFL or WFH z score < –2, WHO LFA or HFA z score < –2); albumin < 3.5 g/dL; ALT > 2 x ULN; ongoing requirement for blood and/or platelet transfusion. After a patient had completed at least 3 months of treatment, suboptimal response was defined as any clinically important manifestation of LAL deficiency (on clinical examination, laboratory assessment, or imaging) that had not improved from baseline, had improved and plateaued (based on at least three assessments) but had not yet normalized, or failed to normalize within 12 months of treatment. Examples of a suboptimal response could include but were not restricted to: a decrease in WFA crossing more than two major centiles, serum transaminase levels meeting the above criteria, albumin < 3.5 g/dL, or the presence of hepatomegaly, splenomegaly, or lymphadenopathy.

[f] Patients on long-term treatment (at least 96 weeks) who had been on a stable dose of sebelipase alfa for at least 24 weeks could be considered for a reduction in infusion frequency to every-other-week infusions of sebelipase alfa. Such patients received sebelipase alfa at the same dose (per infusion) that they had been receiving on their stable once-weekly dosing schedule. Any patient receiving every-other-week dosing who subsequently met criteria for a suboptimal clinical response was to either revert to his/her stable once-weekly dosing schedule or, if applicable, escalate in dose from 1 mg/kg every other week to 3 mg/kg every other week.

[g] If the patient continues to have evidence of suboptimal response after at least four infusions at a dose of 3 mg/kg once weekly, the Investigator, in consultation with the manufacturer and Safety Committee, may consider increasing the dose up to a maximum of 5 mg/kg once weekly when there is evidence of a loss of efficacy due to the potential development of neutralizing antibodies.

Source: Burton et al.;[16] Jones et al.;[17] ARISE CSR;[22] VITAL CSR.[9]

Included Studies

Description of Studies

Two manufacturer-provided trials, ARISE and VITAL, met the inclusion criteria for this review.

The ARISE trial (N = 66), was a phase III, randomized, double-blind, placebo-controlled, multi-centre study that compared the safety and efficacy of sebelipase alfa with placebo in patients with LAL deficiency. The ARISE trial consisted of a screening period of up to six weeks, a 20-week double-blind treatment period, an open-label (OL) period of up to 130 weeks, and a follow-up phone call at least four weeks after the last dose of study drug. Patients were randomized to treatment following completion of all screening assessments and confirmation of study eligibility. Randomization was stratified by: age at randomization (< 12 years versus ≥ 12 years); average screening alanine aminotransferase (ALT) level (< 3 times the upper limit of normal [ULN] versus ≥ 3 times ULN); and use of LLMs (yes, no). Within each of the eight possible combinations of stratification factors, patients were randomly allocated via an interactive voice response system or interactive Web response system in a 1:1 ratio to sebelipase alfa or placebo during the 20-week double-blind period.

After completing the double-blind period, each patient was to begin OL treatment with sebelipase alfa.

The VITAL trial (N = 9), was a phase II/III, open-label, multi-centre, dose-escalation, single-arm (historical cohort controlled) study that evaluated the efficacy and safety of sebelipase alfa in patients who presented with LAL deficiency as infants and were considered to have rapidly progressive disease based primarily on the presence of growth failure within the first six months of life. The VITAL trial consisted of a screening period of up to three weeks, a treatment period of up to four years, and a follow-up visit at least 30 days after the last dose of sebelipase alfa.

Populations

Inclusion and exclusion criteria

In the ARISE trial, eligible patients were at least four years of age on the date of informed consent; had LAL enzyme activity deficiency confirmed by dried blood spot testing at screening, based on the definition of deficiency provided by the central laboratory performing the assay; and had an ALT of greater than and equal to 1.5 times ULN, based on the age- and gender-specific normal ranges of the central laboratory performing the assay on two consecutive screening ALT measurements obtained at least one week apart. The ARISE trial excluded patients who had severe hepatic dysfunction (Child-Pugh Class C) or who had other medical conditions or comorbidities that in the opinion of the Investigator would have interfered with study adherence or data interpretation, including but not restricted to severe intercurrent illness, known causes of active liver disease other than LAL deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excessive alcohol consumption), HIV, poorly-controlled diabetes, or cancers other than non-melanoma skin cancer. Patients were also excluded if they had previous hematopoietic or liver transplant procedure, received treatment with high-dose corticosteroids, or had a known hypersensitivity to eggs (sebelipase alfa is produced in the egg whites of genetically engineered chickens).

In the VITAL trial, eligible patients were male or female children with documented decreased LAL enzyme activity relative to the normal range of the laboratory performing the assay or documented result of molecular genetic testing (2 mutations) confirming a diagnosis of LAL deficiency who were 24 months of age or younger (patients who were older than 8 months of age on the date of first infusion were not eligible for the primary efficacy analysis). Patients had to have growth failure with onset before six months of age, as defined by weight decreasing across at least two of the 11 major centiles on a standard World Health Organization (WHO) weight-for-age (WFA) chart (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th); or body weight in kg below the 10th centile on a standard WHO WFA chart and no weight gain for the two weeks prior to screening; or loss of at least of 5% of birth weight in a child who is older than two weeks of age. If a patient had a rapidly progressive course of LAL deficiency but did not meet the growth failure criteria as defined above, the patient could be enrolled in the study if the Investigator had substantial clinical concerns based on evidence of rapid disease progression that required urgent medical intervention. The VITAL trial excluded patients who had a clinically important concurrent disease or comorbidities [redacted]. Patients were also excluded if they were at least 24 months of age, had

myeloablative preparation or other systemic pre-transplant conditioning for hematopoietic stem cell or liver transplantation, had previous hematopoietic stem cell or liver transplant, or had known hypersensitivity to eggs.

Baseline characteristics

In the ARISE trial, the sebelipase alfa and placebo groups were well balanced with regard to demographic and baseline characteristics (Table 4). Overall, 71% of patients were younger than 18 years of age at randomization (mean and median age at randomization 16.1 years and 13.0 years, respectively) Overall, 39% of patients had received at least one prior LLM. The median age at onset of the first LAL deficiency-related abnormalities was 5 years and 4 years in the sebelipase alfa and placebo groups, respectively. All patients with baseline biopsies (32 of 32, 100%) had evidence of fibrosis. Fifteen of 19 patients in the sebelipase alfa group and 10 of 13 patients in the placebo group had Ishak scores greater than 2. A total of five (26%) of 19 patients in the sebelipase alfa group and five (38%) of 13 patients in the placebo group with biopsy data available for analysis had Ishak fibrosis scores of 5 (indicating either early or incomplete cirrhosis), or 6 (indicating probable or definite cirrhosis). All patients had an ALT greater than 1.5 times ULN at baseline. In the sebelipase alfa and placebo groups, mean baseline ALT values were 105.1 U/L and 99.0 U/L, respectively. Baseline assessments of lipids demonstrated marked dyslipidemia. Mean LDL-C values were 189.9 mg/dL (4.9 mmol/L) and 229.5 mg/dL (5.9 mmol/L) in the sebelipase alfa and placebo groups, respectively. Overall, more than half (58%) of patients had LDL-C values in the very high range (> 190 mg/dL).

In the VITAL trial, the study population was 56% male and 44% female (Table 5). Median age at initiation of treatment with sebelipase alfa was 3.0 months (range 1.1 months to 5.8 months). All patients had confirmed LAL deficiency based on LAL enzyme activity measured in peripheral blood mononuclear cells and/or in a reconstituted dried blood spot. Initial signs and symptoms of LAL deficiency reported for all patients included hepatosplenomegaly, abdominal distension, vomiting, diarrhea, adrenal calcification, and failure to thrive. Other frequent medical history findings were ascites (4 patients), anemia (6 patients), and thrombocytopenia
(3 patients). Three patients had medical history findings suggestive of multiple organ dysfunction syndrome. Eight patients had confirmed growth failure within the first 6 months of life, with seven having a decrease in weight across at least two major centiles since birth. One other patient had other evidence of rapidly progressive disease requiring urgent medical intervention, including marked abdominal distension since eight weeks of age; a medical history of ascites, vomiting, and diarrhea; and massive hepatosplenomegaly, anemia, hypoalbuminemia, and elevated aspartate aminotransferase (AST) and lactate dehydrogenase at screening.

Table 4: Summary of Baseline Characteristics for the ARISE Trial

	ARISE	
	Sebelipase Alfa (N = 36)	Placebo (N = 30)
Age at randomization (in years)		
Mean (SD)	16.9 (11.57)	15.2 (10.23)
Median (range)	13.5 (4 to 55)	13.0 (4 to 58)
≥ 18 years, n (%)	13 (36)	6 (20)
Gender, n (%)		
Male	18 (50)	15 (50)
Female	18 (50)	15 (50)
Race, n (%)		
White	27 (75)	28 (93)
Other	9 (25)	2 (7)
Age at first onset of LAL deficiency-related abnormality (in years)		
Mean (SD)	7.5 (8.36)	5.4 (5.16)
Median (range)	5.0 (0 to 42)	4.0 (0 to 20)
Genetic mutation category		
Homozygous for common mutation, i.e., c.894 G > A	11 (31)	10 (33)
Heterozygous for common mutation	17 (47)	18 (60)
Other mutation[a]	8 (22)	2 (7)
ALT (U/L) at baseline		
Mean (SD)	105.1 (45.31)	99.0 (42.23)
Median (range)	90.0 (52 to 212)	86.5 (50 to 237)
≥ 3 x ULN, n (%)	10 (28)	8 (27)
AST (U/L) at baseline		
Mean (SD)	86.6 (33.49)	78.2 (34.93)
Median (range)	74.5 (41 to 173)	71.0 (39 to 220)
≥ 3 x ULN, n (%)	7 (19)	2 (7)
GGT (U/L) at baseline		
Mean (SD)	52.4 (46.51)	52.0 (60.20)
Median (range)	37.5 (14 to 239)	34.0 (13 to 333)
LDL-C (mg/dL) at baseline		
Mean (SD)	189.9 (57.16)	229.5 (69.95)
Median (range)	193.0 (70 to 280)	213.0 (135 to 378)
≥ 190 mg/dL, n (%)	18 (50)	20 (67)
Non-HDL-C (mg/dL) at baseline		
Mean (SD)	220.5 (61.48)	263.8 (75.48)
Median (range)	223.5 (93 to 332)	241.5 (155 to 408)
TG (mg/dL) at baseline		
Mean (SD)	152.8 (54.43)	174.4 (65.90)
Median (range)	138.0 (65 to 307)	170.0 (66 to 361)
≥ 200 to < 500 mg/dL, n (%)	6 (17)	8 (27)
Cholesterol (mg/dL) at baseline		
Mean (SD)	252.5 (60.70)	296.7 (75.38)
Median (range)	253.0 (121 to 355)	278.0 (191 to 440)

	ARISE	
	Sebelipase Alfa (N = 36)	Placebo (N = 30)
HDL-C (mg/dL) at baseline		
Mean (SD)	32.4 (7.09)	33.4 (7.46)
Median (range)	32.0 (18 to 48)	33.5 (16 to 47)
Liver biopsy, n/N (%)[b]		
Fibrosis	19/19 (100)	13/13 (100)
Bridging fibrosis	10/19 (53)	5/13 (38)
Cirrhosis	5/19 (26)	5/13 (38)
History of LLM use, n (%)		
Patients with at least one prior medication	15 (42)	11 (37)
Patients with at least one prior statin	15 (42)	9 (30)
[redacted]	[redacted]	[redacted]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; LAL = lysosomal acid lipase; LDL-C = low-density lipoprotein cholesterol; LLM = lipid-lowering medication; SD = standard deviation; TG = triglyceride; ULN = upper limit of normal.

[a] Other mutation: At least one of the alleles had an identified mutation but neither allele had the common mutation (i.e., c.894 G > A).

[b] For patients who were ≥ 18 years of age, liver biopsies were obtained at screening and week 20. For patients who were < 18 years of age, liver biopsies were obtained on an optional basis at screening. Fibrosis was defined by an Ishak score of 1 or more, on a scale from 0 to 6, with higher scores indicating a greater degree of fibrosis. Bridging fibrosis was defined by an Ishak score of 3 or 4, and cirrhosis by an Ishak score of 5 or 6.
Source: Burton et al.;[16] ARISE CSR.[22]

Table 5: Summary of Baseline Characteristics for the VITAL Trial

	VITAL
	Sebelipase Alfa (N = 9)
Age at treatment initiation in months	
Median (range)	3.0 (1.1 to 5.8)
Gender, n (%)	
Male	5 (56)
Female	4 (44)
Race, n (%)	
White	4 (44)
Unknown[a]	3 (33)
[redacted]	[redacted]
Age at symptom onset, months	
Range	0 to 5.0
Age at diagnosis, months	
Range	0 to 5.8
LAL-D manifestations, n (%)	
Hepatosplenomegaly	9 (100)
Abdominal distension	9 (100)
Vomiting	9 (100)
Diarrhea	9 (100)
Adrenal calcifications	9 (100)
Failure to thrive	9 (100)
Anemia	6 (67)

	VITAL
	Sebelipase Alfa (N = 9)
Ascites	4 (44)
Thrombocytopenia (< 150 × 10^9/L)	3 (33)
Hematological parameters, median (range)	
Hemoglobin, g/L	93 (1.4 to 103.0)
Platelets, 10^9/L	173 (2.6 to 563)
Serum ferritin, mcg/L, median (range)	586 (253 to 48,740)
Multiple organ dysfunction syndrome, n (%)	3 (33)
Growth failure/entry criteria met,[b] n (%)	
Weight decreasing across ≥ 2 of the 11 major centiles	7 (78)
Body weight <10th centile and no weight increase during 2 weeks before screening	1 (11)
Loss of > 5% of birth weight after 2 weeks of age	0
Rapidly progressive course of LAL-D without meeting growth failure criteria	1 (11)

LAL-D = lysosomal acid lipase deficiency.

[a] Race was not reported for three patients enrolled and treated in France in compliance with that country's regulations.

[b] Patients were required to meet at least one of these criteria.

Source: Jones et al.;[17] VITAL CSR.[9]

Interventions

In the ARISE trial, during the double-blind period (week 0 to week 20), patients either received sebelipase alfa 1 mg/kg or matched placebo (buffered solution identical in composition to the formulation buffer for sebelipase alfa) via IV infusion every other week according to their randomized treatment assignment. During the OL period (week 22 to study completion), all patients were planned to receive sebelipase alfa 1 mg/kg via IV infusion every other week, regardless of their treatment allocation during the double-blind period. No sebelipase alfa dose adjustments (increase or decrease) were permitted during the double-blind period. Patients who were on a stable dosing regimen of an LLM, ursodeoxycholic acid, metformin, glitazones, or vitamin E at the time of screening, were to remain on the dosing regimen for at least 32 weeks of treatment in the study.

In the VITAL trial, patients received a starting dose of sebelipase alfa of 0.35 mg/kg weekly and were considered for a dose escalation to 1 mg/kg weekly once acceptable safety and tolerability had been demonstrated during at least two infusions at the dose of 0.35 mg/kg weekly. Any patient who met the criteria for a suboptimal clinical response after receiving at least four infusions at a dose of 1 mg/kg weekly was considered for further dose escalation to 3 mg/kg weekly. All dose escalations were contingent upon acceptable safety and tolerability during preceding study infusions. [redacted] If a patient continued to have evidence of suboptimal response after at least four infusions at a dose of 3 mg/kg weekly, the Investigator, in consultation with the manufacturer and Safety Committee, could consider increasing the dose up to a maximum of 5 mg/kg weekly when

there was evidence of a loss of efficacy due to the potential development of neutralizing antibodies.

In the VITAL trial, within a patient's first 3 months of treatment, suboptimal response for the purpose of dose adjustment was defined as meeting at least two of the following criteria:

- Failure to gain an average of 5 g/kg body weight per day, and the presence of either of the following:
  - WHO weight-for-length (WFL) or weight-for-height (WFH) z score less than –2
  - WHO length-for-age (LFA) or height-for-age (HFA) z score less than –2
- Albumin less than 3.5 g/dL
- ALT greater than two times ULN
- Ongoing requirement for blood and/or platelet transfusion

After a patient had completed at least three months of treatment, suboptimal response was defined as any clinically important manifestation of LAL deficiency (on clinical examination, laboratory assessment, or imaging) that had not improved from baseline, had improved and plateaued (based on at least three assessments) but had not yet normalized, or failed to normalize within 12 months of treatment. Examples of a suboptimal response could include but were not restricted to, a decrease in WFA crossing more than two major centiles, serum transaminase levels meeting the above criteria, albumin less than 3.5 g/dL, or the presence of hepatomegaly, splenomegaly, or lymphadenopathy. There were no prohibited concomitant medications/therapies in the VITAL trial. Premedication (e.g., oral antihistamines or antipyretics) was not routinely administered prior to study infusions but was recommended in patients who had experienced infusion-associated reactions (IARs) during a previous infusion.

Outcomes

In the ARISE trial, the primary efficacy outcome measure was the proportion of patients who achieved ALT normalization (i.e., ALT below the age- and gender-specific ULN provided by the central laboratory performing the assay) at the end of the double-blind period (week 20). The following secondary efficacy end points were also assessed in the ARISE trial:

- Relative reduction (percentage change from baseline) in LDL-C at the end of the double-blind period
- Relative reduction (percentage change from baseline) in non-HDL-C at the end of the double-blind period
- Proportion of patients with an abnormal baseline AST (i.e., > ULN) who achieved normalization of AST, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay at the end of the double-blind period
- Relative reduction (percentage change from baseline) in TG at the end of the double-blind period
- Relative increase (percentage change from baseline) in HDL-C at the end of the double-blind period
- Relative reduction (percentage change from baseline) in liver fat content (assessed as multi-echo gradient-echo proton density fat fraction in the subset of patients for whom this assessment was performed) at the end of the double-blind period

In the ARISE trial, longitudinal changes in anthropometric data were also summarized using z scores and percentiles for WFA and stature-for age (SFA).

In the VITAL trial, the primary efficacy end point was the proportion of patients surviving to 12 months of age. The following secondary efficacy end points were also assessed in the VITAL trial:

- Proportion of patients surviving at 18 months and 24 months of age
- Median age at death
- Changes from baseline in percentiles and/or z scores as determined from WHO criteria for
  - WFA
  - LFA and/or HFA
- Changes from baseline in ALT
- Changes from baseline in AST

The health-related quality of life (HRQoL) outcome variables in the ARISE trial included changes from baseline in scores for the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, Chronic Liver Disease Questionnaire (CLDQ), and Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales, as appropriate to the age of the patient, where FACIT-F and CLDQ were completed by patients who were at least 17 years of age at the date that informed consent was obtained, while PedsQL was completed by patients who were in the age group of 5 years of age to less than 18 years of age at the date that informed consent was obtained. All of these HRQoL outcomes were exploratory end points in the in the ARISE trial. The VITAL trial did not assess HRQoL.

The Chronic Liver Disease Questionnaire (CLDQ)
The CLDQ is a HRQoL instrument for patients with chronic liver disease. It includes 29 items in the following six domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.[23,24] A 7-point Likert scale is used to grade the response to each item, in which 1 point indicates the worst and 7 points the best possible function.[23,24] Each domain score is calculated by dividing the total of the scores for each item in the domain by the number of items in the domain.[23] Higher CLDQ scores indicate less HRQoL impairment.[24] Younossi et al.[23] reported that a change of 0.5 on the scale from 1 to 7 would signify an important difference in score; however, there is no indication that this was validated using conventional methods for estimating a minimal clinically important difference (MCID).[23] No MCID was identified for patients with LAL deficiency.

The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)
The FACIT-F scale is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function. The fatigue subscale has a seven-day recall period and includes 13 items scored using a 4-point Likert scale (subscale score range 0 to 52).[25] Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best).[25,26] Alternatively, the Trial Outcome Index score may be calculated by summing the physical well-being, functional well-being, and fatigue subscales.[26] Although no information on the validity of FACIT-F or its MCID in patients with LAL deficiency was identified, the MCID for the Functional Assessment of Cancer Therapy (FACT)-General total score ranged from 3 points to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 points to 4 points in rheumatoid arthritis patients.[26,27]

Pediatric Quality of Life Inventory (PedsQL)

The original PedsQL was developed as a HRQoL measure that addressed the paucity of appropriately validated and reliable instruments incorporating both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates both generic and disease/symptom-specific items that are appropriate for the assessment of pediatric chronic conditions.[28] The PedsQL Generic Core Scales are comprised of 23 items under the following modules: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items).[29] These Generic Core Scales are comprised of both the parent proxy-report and the child self-report formats that assess health perceptions. The questions ask how much of a problem each item has been in the past month. A 5-point Likert response scale is used across the child reports (from ages 8 years to 18 years) and the corresponding parent report, and include the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a 3-point scale is used for simplification and ease of use for children who are aged five years to seven years and include 0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem, with each of the response choices anchored to a happy-to-sad faces scale.[29] The scores, which are reversed scored, are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0 with higher scores indicative of a higher HRQoL. The PedsQL Generic Core Scales have been validated and determined to be reliable and responsive in pediatric patients with chronic conditions. The MCID for the Total Scale Score of the child self-report is a change of 4.4, while the MCID for the Total Scale Score for parent proxy-report is a change of 4.5 (assessed in patients with a variety of chronic conditions). However, no MCID was identified in patients with LAL deficiency.

Adverse Events

In the ARISE trial a treatment-emergent adverse event (TEAE) during the double-blind period was defined as an adverse event (AE) whose onset occurred, severity worsens, or intensity increases after the first study drug infusion during the double-blind period. In the VITAL trial, an AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient, whether or not causally related to administration of treatment. In both trials, a serious adverse event (SAE) was any AE that was (or led to) death, immediately life-threatening, required inpatient hospitalization, or prolongation of existing hospitalization, congenital anomaly/birth defect, persistent or significant disability or incapacity, or an important medical event that, based upon appropriate medical judgment, the event jeopardized the patient and or required medical or surgical intervention to prevent one of the previously mentioned outcomes.

Statistical Analysis

ARISE

In the ARISE trial, a sample size of 50 randomized patients (approximately 25 patients per treatment group) was planned to provide greater than 97% power to detect statistically significant differences between sebelipase alfa and placebo for the primary end point (ALT normalization) using Fisher's exact test at alpha = 0.05, and also to provide greater than 90% power to detect statistically significant differences between sebelipase alfa and placebo for reduction in LDL-C, reduction in non-HDL-C, normalization of AST, and reduction in TG. The following secondary efficacy end points were compared using a Wilcoxon rank sum test, based on the fixed hypothesis sequence (at alpha = 0.05): relative

reduction in LDL-C, relative reduction in non-HDL-C, relative reduction in TG, relative increase in HDL-C, and relative reduction in liver fat content. The secondary efficacy end point proportion of patients with an abnormal baseline AST (i.e., > ULN) who achieved normalization of AST, was compared between treatment groups using Fisher's exact test, based on the fixed hypothesis sequence (at alpha = 0.05). Efficacy analyses were performed primarily on the full analysis set (FAS). For all end points, if a patient had more than one post-baseline assessment during the double-blind period, the last post-baseline assessment (called the "Last DB Assessment") was used to determine the value at the end of the double-blind period. For continuous end points (relative reduction from baseline), a patient's last post-baseline assessment was used, regardless of treatment adherence. No imputation of missing data was performed for the efficacy parameters.

Longitudinal changes in anthropometric data were summarized using z scores and percentiles for WFA and SFA, determined from publicly available US Centers for Disease Control and Prevention growth curves for patients who were 18 years of age and younger. Baseline age-normalized percentiles for height were also summarized in older patients who were at least 18 years of age.

Age at randomization, genetic mutation category (ad hoc analyses), and fibrosis/cirrhosis (ad hoc analyses) were used for subgroup analyses of the primary and secondary efficacy end points.

In order to control the type I error rate it was planned that if the primary analysis of the primary end point was statistically significant at alpha = 0.05, then statistical hypothesis tests of the secondary end points would be performed in a fixed sequence as outlined below. If any test was statistically significant at alpha = 0.05, then the next statistical hypothesis in the sequence were tested at alpha = 0.05. If at any point in the sequence a particular hypothesis was not statistically significant at alpha = 0.05, then formal statistical hypothesis testing was to be stopped, and none of the remaining tests were to be considered statistically significant. The sequence of hypothesis tests compared sebelipase alfa and placebo with respect to:

- Primary End Point: Proportion of patients who achieved ALT normalization at the end of the double-blind period
- Relative reduction (percentage change from baseline) in LDL-C at the end of the double-blind period
- Relative reduction (percentage change from baseline) in non-HDL-C at the end of the double-blind period
- Proportion of patients with an abnormal baseline AST (i.e., > ULN) who achieved normalization of AST, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay at the end of the double-blind period
- Relative reduction (percentage change from baseline) in TG at the end of the double-blind period
- Relative increase (percentage change from baseline) in HDL-C at the end of the double-blind period
- Relative reduction (percentage change from baseline) in liver fat content (assessed as multi-echo gradient-echo proton density fat fraction in the subset of patients for whom this assessment was performed) at the end of the double-blind period

Descriptive *P* values of group differences using Wilcoxon rank sum test were provided for change from baseline for each visit for the exploratory efficacy end points: CLDQ total score, FACIT-F total score, and PedsQL Generic Core Scales total score.

VITAL

In the VITAL trial, the primary efficacy end point is the proportion of patients in the Primary Efficacy Set surviving to 12 months of age. [redacted][8,9] The LAL-1-NH01 study, which was ongoing at the time of the calculation of the sample size for the VITAL trial, was a retrospective natural history study that included untreated children diagnosed with LAL deficiency prior to two years of age. For the purposes of calculating the sample size in the VITAL trial, an interim analysis of LAL-1-NH01 suggested that of the 18 patients who met early growth failure criteria and had known date of death, only one patient survived past 12 months of age. An exact 95% confidence interval (CI) for survival past 12 months of age in these patients is (0.14% to 27.29%). Hence if the lower limit of an exact 95% CI for the 12-month survival rate in the VITAL trial is higher than 27.29%, there would be statistical evidence that the rate of 12-month survival in the VITAL trial is superior to that in study LAL-1-NH01 for a similar patient population. Therefore, if eight patients were included in the primary efficacy analysis and six of these patients survive to 12 months of age, the exact 95% CI for 12-month survival would be (34.91% to 96.81%) with the lower limit exceeding the upper limit of the CI for study LAL-1-NH01. No other comparisons were planned in the VITAL trial. The proportion of patients surviving to 12 months of age was calculated, along with an exact 95% CI based on the Clopper-Pearson method. A Kaplan–Meier estimate, with exact 95% CI for median survival past the first infusion of sebelipase alfa was also provided. [redacted]

Analysis Populations

ARISE

Efficacy analyses were performed primarily on the FAS, defined as patients who were randomized to treatment and received at least one dose (or any portion of a dose) of sebelipase alfa or placebo. A per-protocol (PP) set was defined as patients in the FAS who did not have any other major protocol violations that would affect interpretation of results for serum transaminases or serum lipids. Secondary efficacy analyses were performed using the PP set. All safety analyses were performed for the FAS. In the unlikely event that a patient inadvertently received one or more infusions of the incorrect study drug, the patient was to be analyzed according to their randomized treatment in the specified safety analyses and additional ad hoc summaries of safety data were to be created in order to fully assess the impact of the incorrect dosing on safety conclusions.

VITAL

The FAS consisted of all patients who received any amount of sebelipase alfa. The primary efficacy analysis set (PES) included patients in the FAS who were no older than eight months of age on the date of the first infusion of sebelipase alfa. The PP analysis set included patients in the PES who received at least four complete infusions of sebelipase alfa. Safety analyses were performed for the FAS.

Patient Disposition

In the ARISE trial, a total of 92 screenings for study eligibility occurred across 86 unique patients. [redacted] Thus, a total of 20 of the 86 unique patients screened were screen failures. Of the 20 unique patients who were determined to be screen failures, the reason was reported as not meeting the entrance criteria for 17 patients and withdrawal of consent for the remaining three patients. Of these 66 patients enrolled, 36 were randomly assigned to the sebelipase alfa group and 30 were assigned to the placebo group. Of the 66 patients enrolled, all 66 (100%) received at least one study drug infusion and thus were included in the FAS. All but one patient completed the double-blind period and continued in the OL period. One patient in the sebelipase alfa group did not complete the double-blind period. [redacted] (Table 6).

In the VITAL trial, 11 patients were screened, two of whom died during screening. The other nine patients were enrolled and treated in the study. As of the data cut-off (May 30, 2014), six patients continue to receive treatment in the study and three patients are considered early terminated due to death prior to 12 months of age (Table 7).

Table 6: Patient Disposition for the ARISE Trial

	ARISE	
	Sebelipase Alfa	**Placebo**
Screened, N	92	
Randomized	36	30
Patients completing double-blind period, n (%)	35 (97)	30 (100)
Patients not completing double-blind period, n (%)	1 (3)	0
Patients discontinuing study during double-blind period	1 (3)	0
Patients entering open-label period, n (%)	35 (97)	30 (100)
Patients continuing in open-label period	35 (97)	30 (100)
FAS, N (%)	36 (100)	30 (100)
PP, N (%)	34 (94)	29 (97)
Safety, N (%)	36 (100)	30 (100)

FAS = full analysis set; PP = per-protocol.
Source: ARISE CSR.[22]

Table 7: Patient Disposition for the VITAL Trial

	Sebelipase Alfa
Patients who signed informed consent form	11
Patients treated (FAS)[a]	9
Patients not treated	2
Treated patients (FAS), n (%)	9 (100)
Ongoing	6 (67)
Early termination	3 (33)
Reason for early termination, n (%)	
Patient death	3 (33)
PES, N (%)[b]	9 (100)
PP, N (%)[c]	7 (78)
Safety, N (%)	9 (100)

FAS = full analysis set; PES = primary efficacy analysis set; PP = per-protocol.
[a] FAS includes patients who received any amount of sebelipase alfa.
[b] Includes patients in the FAS who were no older than 8 months of age on the date of the first infusion of sebelipase alfa.
[c] Patients in the PES who, in addition, received at least four complete infusions of sebelipase alfa.
Source: VITAL CSR.[9]

Exposure to Study Treatments

In the ARISE trial, 35 of 36 patients in the sebelipase alfa group and 29 of 30 patients in the placebo group received all 11 study drug infusions during the double-blind treatment period, as planned (Table 8). [redacted]

In the VITAL trial, as of the data cut-off (June 10, 2014), the nine patients in the PES have received a total of 462 infusions of sebelipase alfa over a combined treatment period [redacted]. The majority of these infusions have been administered at a dose of 1 mg/kg (141 infusions) or 3 mg/kg (295 infusions). All six surviving patients received a dose escalation to 3 mg/kg weekly based on clinical response, and one patient received a further dose escalation to 5 mg/kg weekly due to a continued slow growth response observed in association with the presence of neutralizing antibodies (Table 9). One patient on long-term treatment was transitioned to an every-other-week regimen but subsequently reverted to a weekly regimen following a worsening of serum transaminases.

Table 8: Study Drug Exposure in the ARISE trial (FAS, Double-Blind Treatment Period)

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

FAS = full analysis set.
Source: ARISE CSR.[22]

Table 9: Study Drug Exposure (Full Analysis Set) in the VITAL Trial

	VITAL
	Sebelipase Alfa (N = 9)
Number of Weeks on Study	
Total number of weeks	[redacted]
Mean (SD) weeks per patient	[redacted]
Median (range)	60.29 (0.1, 164.7)
Total Number of Infusions	
Total number of infusions	462
Total number of patients	9
Mean (SD) infusions per patient	[redacted]
Median (range)	[redacted]
Total Number of Infusions at 0.35 mg/kg	
Total number of infusions	[redacted]
Total number of patients	[redacted]
Mean (SD) infusions per patient	[redacted]
Median (range)	[redacted]
Total Number of Infusions at 1.0 mg/kg	
Total number of infusions	141
Total number of patients	[redacted]
Mean (SD) infusions per patient	[redacted]
Median (range)	[redacted]
Total Number of Infusions at 3.0 mg/kg	
Total number of infusions	295
Total number of patients	[redacted]
Mean (SD) infusions per patient	[redacted]
Median (range)	[redacted]

	VITAL
	Sebelipase Alfa (N = 9)
Total Number of Infusions at 5.0 mg/kg	
Total number of infusions	8
Total number of patients	1
Mean (SD) infusions per patient	8.0 (NA)
Median (range)	[redacted]
Number of Infusions	
Total	462
0.35 mg/kg q.w.	[redacted]
1.0 mg/kg q.w.	141
1.0 mg/kg q.2.w.	[redacted]
3.0 mg/kg q.w.	[redacted]
3.0 mg/kg q.2.w.	[redacted]
5.0 mg/kg q.w.	8
5.0 mg/kg q.2.w.	[redacted]
Other[a]	[redacted]

FAS = full analysis set; NA = not available; q.w. = every week; q.2.w. = every other week; SD = standard deviation.
[a] One infusion each at doses of 0.2 mg/kg, 0.3 mg/kg, 0.5 mg/kg, and 0.75 mg/kg were given to one patient.
Source: VITAL CSR.[9]

Critical Appraisal

Internal Validity

In the ARISE trial, individual results for sebelipase alfa serum concentrations and anti-drug antibodies (ADA) were not provided to the study sites, or any manufacturer personnel involved in the conduct of the study, until after all data for the double-blind treatment period had been monitored and the database locked for this period. IARs are known complications of enzyme replacement therapy administration, and such reactions could have potentially resulted in an unblinding of the study drug. There were differences in the proportion of patients with IARs (6% in the sebelipase alfa and 13% patients in the placebo group). However, the proportion of patients experiencing these reactions was low (two patients in the sebelipase alfa group and four patients in the placebo group). Therefore, the impact on blinding was likely minimal.

In the ARISE trial, the manufacturer accounted for multiple comparisons using a fixed sequence testing procedure. This testing procedure was followed.

In the ARISE trial, patient-reported outcomes (PRO) were exploratory efficacy end points and there were no multiplicity adjustments applied to the PRO variables, hence results of the PRO (FACIT-F, CLDQ, and PedsQL Generic Core Scales). In addition, there was a lack of data imputation for the PRO data when missing; such missing data are unlikely to be missing at random (usually sicker patients are missing), which could lead to overestimates in HRQoL. In addition, any interpretation of these PRO data has to take into consideration the fact that not the entire study population was eligible to complete the various questionnaires. This is because of the age groups for which these instruments have been validated. For the CLDQ and FACIT-F, only patients who were at least 17 years of age at enrolment could participate [redacted]

[redacted]; for PedsQL, only patients in the age group five years to less than and equal to 18 years at enrolment could participate [redacted]. These very small sample sizes mean that strong inferences cannot be drawn about any between-group differences.

In the ARISE trial, despite randomized group allocation, there were baseline imbalances in several laboratory test parameters, where baseline results for LDL-C, non-HDL-C, TG, cholesterol, HDL-C, and liver biopsy were better in the sebelipase alfa group than in the placebo group, and baseline results for ALT and AST were better in the placebo group that in the sebelipase alfa group. Given that these laboratory test parameters were the primary and secondary efficacy end points in the ARISE trial, these potential imbalances might have influenced results in favour of sebelipase alfa.

The VITAL trial was open-label. Not blinding patients, investigators and outcome assessors is not critical for interpretation of the objective primary end point which was proportion of patients surviving to 12 months of age. On the other hand, being aware of treatment allocation may have influenced reporting of AEs.

The VITAL trial used a historical control cohort (study LAL-1-NH01) to make non-statistical comparisons for the primary outcome (proportion of patients surviving to 12 months of age). To improve comparability between the populations in the two studies, a subpopulation of 21 infants with early growth failure within the first six months of life from study LAL-1-NH01, using similar criteria for defining growth failure as that used in VITAL, were used as historical controls. However, the comparability of the two populations is a concern. The VITAL trial and the LAL-1-NH01 study from which the historical survival rate was derived did not take place in the same time period, where 21 out of 36 patients included in LAL-1-NH01 (the historical control study) were diagnosed before 1995. This opens the possibility that changes in diagnosis and clinical management of LAL deficiency, such as improved best supportive care options, mean that patients in each cohort were likely not at the same baseline at the start of the respective follow-up periods.
The lack of methods to ensure comparisons between patients with similar characteristics in the absence of randomization (e.g., propensity-score matching) exacerbates the uncertainty as to the comparability of the cohorts.

In the VITAL trial, the sample size was very small (only nine patients were enrolled), hence differences in one or two patients can have a substantial impact on survival rate. However, due to the rarity of this disease population such a small sample size is not unusual.

External Validity

In the ARISE trial, a considerable proportion of patients (23%) were screened in the trials but did not enter the treatment phase. The most common reason stated was that the patient did not meet the inclusion criteria. This may largely compromise the generalizability of the results. The ARISE trial also excluded patients who had severe hepatic dysfunction (Child-Pugh Class C); had previous hematopoietic or liver transplant procedure; or who had other medical conditions or comorbidities that in the opinion of the Investigator would have interfered with study adherence or data interpretation, including but not restricted to severe intercurrent illness, known causes of active liver disease other than LAL deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excessive alcohol consumption), HIV, poorly-controlled diabetes, or cancers other than non-melanoma skin cancer. Therefore, the generalizability of the results of the ARISE trial to these populations is unknown. In addition, patients included in the ARISE trial were

at least 4 years of age, ranging from 4 years to 58 years, with the majority of included patients in the 4- to 18-year-old range; hence the generalizability of the results of the ARISE trial to patients outside this age range is unknown.

The clinical expert indicated that the key efficacy outcomes in ARISE should have been hard clinical outcomes and not surrogate outcomes. In the ARISE trial there is no evidence to address long-term and key clinical end points such as the need for liver transplant, cardiovascular events, and death. In addition, for the primary outcome ALT normalization, no data were found showing how it directly measures or correlates with patient functioning, development, and survival. The FDA medical review indicated that "*ALT neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions, or survives) nor represents a surrogate end point reasonably likely to predict clinical benefit in children and adults with CESD.*"[18] The FDA medical review also indicated that "*normal ALT does not necessarily exclude the presence or progression of liver disease*,"[18] and concluded that "*normalization of ALT does not reliably represent a clinical benefit*."[18]. In the VITAL trial there is no evidence to address long-term and key clinical end points such as the need for liver transplant, cardiovascular events, and HRQoL.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 2). See Appendix 4 for detailed efficacy data.

No data were available for the following key efficacy outcomes: patient-reported symptoms, cardiovascular events, and the need for liver transplant in the ARISE trial, as well as the need for liver transplant, cardiovascular events, and HRQoL in the VITAL trial. In addition, no subgroup data were available for the key efficacy outcomes identified in the protocol. Subgroup results by age, genetic mutation category, and presence of cirrhosis were available in the ARISE trial, but no subgroup results were available in the VITAL trial.

Overall Survival

VITAL

The percentage of patients who received any amount of sebelipase alfa and who were no older than eight months of age on the date of the first infusion of sebelipase alfa surviving to 12 months of age was 67% (6 of 9 patients), with an exact 95% CI for survival of 29.93% to 92.51% (Table 10).

[redacted] (Table 10).

A comparison between sebelipase alfa-treated patients who survived to 12 months of age in the VITAL trial with a historical cohort of untreated infants with LAL deficiency suggests improved survival with sebelipase alfa treatment compared with the control cohort (Figure 2). In the historical cohort, 0 of 21 patients survived beyond eight months of age (0% 12-month survival [95% CI, 0% to 16%]). No statistical comparison was undertaken between the survival in the VITAL trial and that in the historical cohort study. No other comparative data were presented for the VITAL trial.

Figure 2: Survival from Birth to 12 Months of Age in the VITAL Trial (LAL-CL03) and the Historical Cohort (LAL-1-NH01)

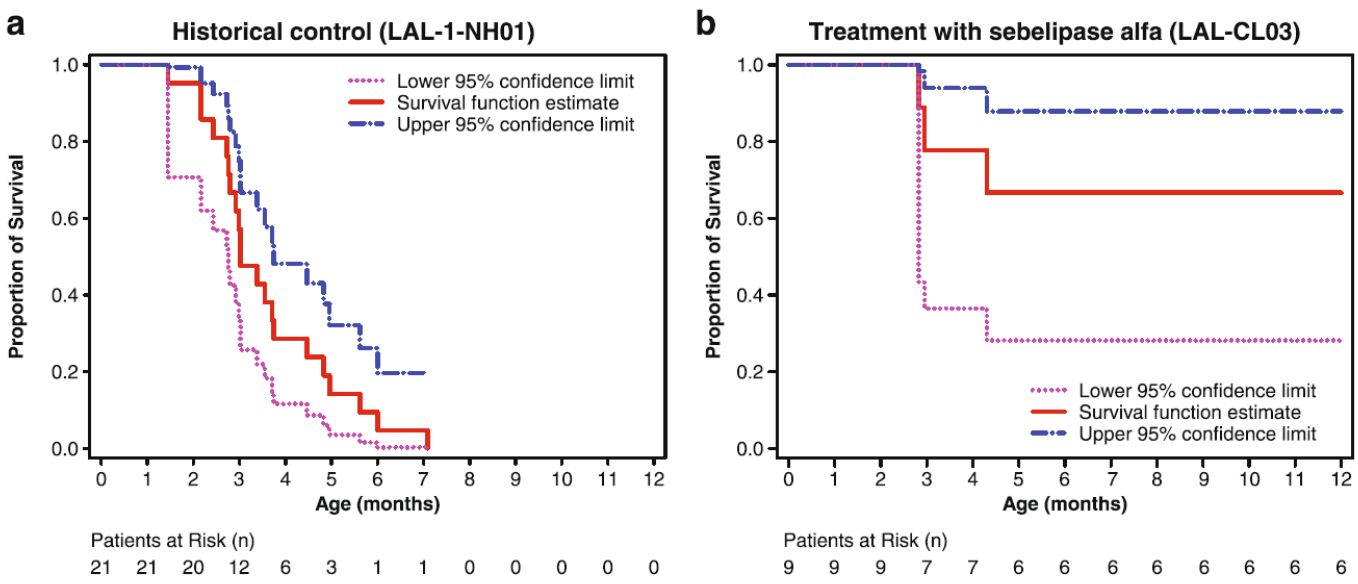

Fig. 2 Survival from birth to 12 months of age. Kaplan-Meier analyses of (**a**) historical control group of untreated patients with early growth failure ($n = 21$) from natural history study of infants with LAL deficiency (LAL-1-NH01; data on file, Alexion Pharmaceuticals, Inc.) [7] and (**b**) the primary efficacy set of the present phase 2/3 study ($N = 9$). Patients in the historical control group were considered untreated if they had not received hematopoietic stem cell transplant, liver transplant, or enzyme replacement therapy. Growth failure was defined by 1) decreased body weight across ≥2 of the 11 major centiles on a standard WHO weight-for-age chart, or 2) body weight in kilograms below the 10th centile on a standard WHO weight-for-age chart and no weight gain for the previous 2 weeks, or 3) loss of ≥5% of birth weight in children who are >2 weeks of age

Source: Reproduced from Jones SA, Rojas-Caro S, Quinn AG, Friedman M, Marulkar S, Ezgu F, et al. "Survival in infants treated with sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multi-centre, dose-escalation study." *Orphanet Journal of Rare Diseases*. 2017 Feb 8;12(1):25, 2017. Creative Commons licence 4.0: https://creativecommons.org/licenses/by/4.0/legalcode

Six of the nine patients in the PES were alive as of the data cut-off for the CSR provided by the manufacturer (June 10, 2014). The ages of these patients at their last available assessment were 12.0, 15.7, 15.8, 20.4, 25.1, and 42.2 months. [redacted]

Three (33.3%) of the nine patients in the PES died [redacted] Cause of death was hepatic failure in one patient, peritoneal hemorrhage in the second patient, and cardiac arrest in the third patient. These deaths were assessed as unrelated to the study drug.

An additional death occurred at 15 months of age due to the patient's other medical conditions (hemoglobin E disease, patent foramen ovale).[7]

ARISE

No deaths were reported in either treatment group in the ARISE trial during the double-blind period.

Table 10: Survival for the VITAL Trial

	VITAL
	Sebelipase Alfa (N = 9)
Survived to 12 Months of Age (PES, N = 9)	
No, n (%)	3 (33)
Yes, n (%)	6 (67)
Per cent surviving (95% CI)[a]	67 (29.93 to 92.51)
Kaplan–Meier estimate of survival to 12 months of age[b], %	67
Survived to 12 months of age (PP analysis set, N = 7)	
No, n (%)	[redacted]
Yes, n (%)	[redacted]
Per cent surviving (95% CI)[a]	[redacted]
Kaplan–Meier estimate of survival to 12 months of age[b], %	[redacted]
Survival to 18 months of age (PES, N = 9)	
No, n (%)[c]	[redacted]
Yes, n (%)	[redacted]
NA, n (%)[d]	[redacted]
Per cent surviving (95% CI)[e]	[redacted]
Kaplan–Meier estimate of survival to 18 months of age, %	[redacted]
Survival to 24 months of age (PES, N = 9)	
No, n (%)[c]	[redacted]
Yes, n (%)	[redacted]
NA, n (%)[d]	[redacted]
Per cent surviving (95% CI)[e]	[redacted]
Kaplan–Meier estimate of survival to 24 months of age , %	[redacted]
Survival to 30 Months of Age (PES, N = 9)	
No, n (%)[c]	[redacted]

	VITAL
	Sebelipase Alfa (N = 9)
Yes, n (%)	[redacted]
NA, n (%)[d]	[redacted]
Per cent surviving (95% CI)[e]	[redacted]
Kaplan–Meier estimate of survival to 30 months of age, %	[redacted]
Survival to 36 Months of Age (PES, N = 9)	
No, n (%)[c]	[redacted]
Yes, n (%)	[redacted]
NA, n (%)[d]	[redacted]
Per cent surviving (95% CI)[e]	[redacted]
Kaplan–Meier estimate of survival to 36 months of age, %	[redacted]
Median age at death in months	[redacted]

CI = confidence interval; NA = not applicable; PES = primary efficacy analysis set; PP = per-protocol.
[a] Exact CI calculated using Clopper-Pearson method.
[b] For this analysis, patients were also censored if they had not reached 12 months of age but were alive and discontinued the study or the study ended before they reached 12 months of age.
[c] Includes patients, if any, who were permanently lost to follow-up prior to the age specified in the analysis.
[d] Patients alive and still on study who have not yet reached the age specified in the analysis. These patients are excluded from the per cent surviving analyses and censored in Kaplan–Meier analyses.
[e] Exact CI calculated using Clopper-Pearson method. Patients with unknown survival status at the age specified in the analysis are excluded.
Source: VITAL CSR.[9]

Health-Related Quality Of Life (HRQoL) and Patient-Reported Symptoms

ARISE

The FACIT-F, CLDQ, and PedsQL were used to collect HRQoL data in the ARISE trial. [redacted] (Table 11).

VITAL

HRQoL was not assessed in the VITAL trial.

Table 11: Patient-Reported Outcomes FACIT-F, CLDQ, and PedsQL in the ARISE Trial

[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; CLDQ = Chronic Liver Disease Questionnaire; PedsQL = Pediatric Quality of Life Inventory.
[a] FACIT-F total score only available for patients who were 17 years or older at date of informed consent. The total score ranges from 0 to 52; a higher value indicates a better quality of life.
[b] Wilcoxon rank sum test for treatment differences.
[c] CLDQ questionnaire only available for patients who were 17 years or older at date of informed consent. Total score ranges from 0 to 7; higher values indicate a better quality of life.
[d] PedsQL questionnaire only available for patients who were 5 years to ≤ 18 years old at date of informed consent. Total score ranges from 0 to 100; higher values indicate a better quality of life.
Source: ARISE CSR.[22]

Anthropometrics

VITAL

In the VITAL trial, at baseline, the median WFA percentile was 3.08 (n = 8), [redacted].

In the VITAL trial, at baseline, the median LFA percentile was 1.80 for the eight patients with available data. [redacted]

[redacted] (Table 13).

ARISE

[redacted]

Table 12: Observed Values and Changes from Baseline in WFA Percentiles for the VITAL Trial (PES)

[redacted]

NA = not applicable; PES = primary efficacy analysis set; SD = standard deviation; WFA = weight-for-age.
[a] Baseline is defined as the last measurement prior to the first infusion of sebelipase alfa.
Source: VITAL CSR.[9]

Table 13: Observed Values and Changes from Baseline in LFA or HFA Percentiles for the VITAL Trial (PES)

[redacted]

HFA = height for age; LFA = length-for-age; NA = not applicable; PES = primary efficacy analysis set; SD = standard deviation.
[a] Baseline is defined as the last measurement prior to the first infusion of sebelipase alfa.
Source: VITAL CSR.[9]

Table 14: Change from Baseline to Week 20 Body Weight, Height and BMI in the ARISE Trial (FAS, Double-Blind Treatment Period)

	[redacted]	
	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

BMI = body mass index; FAS = full analysis set.
Source: ARISE CSR.[22]

Other Efficacy Outcomes

ALT

VITAL

In the VITAL trial, at baseline, individual ALT levels ranged from 16.0 U/L to 297.0 U/L (median = 145.0 U/L) for the nine patients in the PES, and were above the ULN in [redacted] patients. [redacted] ALT levels decreased following initiation of treatment with sebelipase alfa. By week 4, two weeks after most patients escalated to 1 mg/kg weekly, the median (range) reduction in ALT was −33.0 U/L (−226.0 U/L to −4.0 U/L, n = 5), however by week 60, the median (range) reduction in ALT was −10.50 U/L (−118.0 U/L to 26.0 U/L, n = 4) (Table 16).

ARISE

In the ARISE trial, a greater percentage of patients in the sebelipase alfa group (31%, 11 patients out of 36 patients) than in the placebo group (7%, 2 patients out of 30 patients) achieved normalization in ALT, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay. By the last time point in the double-blind period, there was a 24% difference between groups in favour of sebelipase alfa. The difference between groups was statistically significant (*P* = 0.0271) (Table 18).

AST

VITAL

In the VITAL trial, at baseline, individual AST levels ranged from 71.0 U/L to 716.0 U/L (median = 125 U/L) for the nine patients in the PES, and were above the ULN in all [redacted] patients. [redacted]. By week 4, two weeks after most patients escalated to 1 mg/kg weekly, the median (range) reduction in AST was −55.5 U/L (−427.0 U/L to −20.0 U/L, n = 4). Thereafter, AST remained fairly stable through week 60, the last assessment for which data were available for more than one patient, with a few patients having fluctuations in AST over time (Table 17).

ARISE

In the ARISE trial, a greater percentage of patients in the sebelipase alfa group (42%, 15 out of 36 patients) than in the placebo group (3%, 1 out of 29 patients) experienced normalization in AST, based on age- and gender-specific normal ranges provided by the central laboratory performing this assay. By the last time point in the double-blind period, there was a 39% difference between groups in favour of sebelipase alfa. The difference between groups was statistically significant (*P* = 0.0003) (Table 18).

LDL-C

VITAL

In the VITAL trial, baseline LDL levels ranged [redacted]

ARISE

In the ARISE trial, a greater mean per cent change from baseline in LDL-C was seen in the sebelipase alfa group than in the placebo group (−28.42% versus −6.25%, respectively); a −22.17% difference between groups in favour of sebelipase alfa. The difference between groups was statistically significant (*P* < 0.0001) (Table 18).

HDL-C

VITAL

In the VITAL trial, baseline HDL levels ranged [redacted]

ARISE

In the ARISE trial, a greater mean per cent increase from baseline to the last time point in the double-blind period in HDL-C was seen in the sebelipase alfa group than in the placebo group (19.57% versus −0.29%, respectively); a 19.86% difference between groups in favour of sebelipase alfa. This difference between groups was statistically significant ($P < 0.0001$) (Table 18).

Non-HDL-C

VITAL

This outcome was not assessed in the VITAL trial.

ARISE

In the ARISE trial, a greater mean per cent reduction from baseline to the last time point in the double-blind period in non-HDL-C was seen in the sebelipase alfa group than in the placebo group (−27.97% versus −6.94%, respectively); a −21.04% difference between groups in favour of sebelipase alfa. The difference between groups was statistically significant ($P < 0.0001$) (Table 18).

Triglyceride

VITAL

In the VITAL trial, baseline TG levels ranged from [redacted]

ARISE

In the ARISE trial, a greater mean per cent decrease from baseline to the last time point in the double-blind period in TG was seen in the sebelipase alfa group than in the placebo group (−25.45% versus −11.14%, respectively); a −14.30% difference between groups in favour of sebelipase alfa. The difference between groups was statistically significant ($P = 0.0375$). (Table 18).

Liver Fat Content

VITAL

Liver fat content was not assessed in the VITAL trial.

ARISE

In the ARISE trial, a greater mean per cent decrease from baseline to the last time point in the double-blind period in liver fat content was seen in the sebelipase alfa group than in the placebo group (−31.98% versus −4.21%, respectively); a −27.77% difference between groups in favour of sebelipase alfa. This difference between groups was statistically significant ($P < 0.0001$) (Table 18).

Subgroup Analyses

VITAL

No subgroup analysis was undertaken in the VITAL trial.

ARISE

Subgroup analyses by age at randomization, genetic mutation category, and presence of cirrhosis were undertaken in the ARISE trial for the following outcomes: ALT normalization, LDL reduction, non-HDL-C reduction, AST normalization, TG reduction, HDL-C increase, and liver fat content reduction.

[redacted]

[redacted]

Harms

Only those harms identified in the review protocol are reported below (Methods).

Adverse Events

In the VITAL trial, all patients reported at least one TEAE. The most frequently reported TEAE, i.e., those reported for at least two patients and/or greater than three events (irrespective of the number of patients) were: vomiting (20 events in 6 [67%] patients), diarrhea (17 events in 6 [67%] patients), pyrexia (26 events in 5 [56%] patients), rhinitis (7 events in 5 [56%] patients), anemia (5 events in 4 [44%] patients), cough (11 events in 3 [33%] patients), catheter-site infection (6 events in 3 [33%] patients), device-related infection (6 events in 3 [33%] patients), diaper-associated dermatitis (6 events in 3 [33%] patients), nasopharyngitis (5 events in 3 [33%] patients), urticaria (4 events in 3 [33%] patients), tachycardia (6 events in 2 [22%] patients), rash (4 events in 2 [22%] patients), chills (4 events in 1 [11%] patients), and decreased appetite (4 events in 1 [11%] patients) (Table 15).

In the ARISE trial, 86% of patients in the sebelipase alfa group and 93% of patients in the placebo group reported at least one TEAE during the double-blind period. The most common (≥ 10% incidence) TEAEs reported during the double-blind period in the sebelipase alfa group with corresponding incidence in the placebo group were: headache (28% and 20%, respectively), pyrexia (19% and 20%, respectively), upper respiratory infection (17% and 20%, respectively), diarrhea (17% in each group), oropharyngeal pain (17% and 3%, respectively), epistaxis (11% and 20%, respectively), and nasopharyngitis (11% and 10%, respectively) (Table 15).

Serious Adverse Events

In the VITAL trial, a total of 31 SAEs were reported for 8 (89%) patients (Table 15). One patient experienced SAEs that were assessed as related to the study drug. This patient developed serious IARs of grade 3 tachycardia and pallor and grade 2 chills and pyrexia on day 84 (week 12), while receiving treatment with sebelipase alfa at a dose of 3 mg/kg weekly. All four SAEs resolved the same day following interruption of the sebelipase alfa infusion and administration of antihistamine, antipyretic, and IV sodium chloride. All other SAEs reported in this study were assessed as unrelated to the study drug.

In the ARISE trial, 6% of patients in the sebelipase alfa group and 3% of patients in the placebo group experiencing an SAE (Table 15). No particular SAE was reported in more than one patient. SAEs reported among sebelipase alfa-treated patients included gastritis and infusion-related reaction. The only SAE reported among the placebo-treated patients was road traffic accident.

Withdrawal Due to Adverse Events

In the VITAL trial, as of the data cut-off for the CSR provided by the manufacturer (June 10, 2014), no patient had discontinued from the study due to TEAEs. One patient was discontinued from treatment after the first infusion (week 0) due to a TEAE of bradycardia that was unrelated to the study drug. This patient subsequently died of hepatic failure prior to the next scheduled infusion at week 1.

In the ARISE trial, one patient in the sebelipase alfa group discontinued from the double-blind period because of an IAR. No other patient discontinued from the double-blind period because of an IAR or other TEAE.

Mortality

In the VITAL trial, three patients died prior to the data cut-off for the CSR provided by the manufacturer (June 10, 2014), due to complications related to disease progression or a non-study related procedure [redacted] These patients died at approximately three months of age due to hepatic failure and peritoneal hemorrhage (following abdominal paracentesis due to increased ascites), respectively. [redacted] All deaths were assessed by the Investigator as unrelated to the study treatment.

In the ARISE trial, no deaths occurred during the double-blind period (Table 15).

Notable Harms

In the VITAL trial, four (44%) of the nine patients (or 67% of the six patients receiving more than four infusions) experienced a total of 47 IARs, most commonly involving pyrexia or vomiting, [redacted] Anaphylaxis was not reported in any patient treated with sebelipase alfa in this study. Post-treatment immunogenicity data were available for seven patients. Of these seven patients, four (57%) were ADA positive during at least one assessment. [redacted] Chest discomfort, headache, and anxiety were not reported in any patient. Tachycardia was reported in two (22%) patients.

In the ARISE trial, the incidence of IARs was lower in the sebelipase alfa group (6%) than in the placebo group (13%). As stated above, the IAR in one patient in the sebelipase alfa group was considered to be an SAE. [redacted]

Table 15: Harms

	ARISE		VITAL
AEs	**Sebelipase Alfa (N = 36)**	**Placebo (N = 30)**	**Sebelipase Alfa (N = 9)**
Patients with > 0 AEs, N (%)	31 (86)	28 (93)	9 (100)
Most common AEs[a]			
Headache	10 (28)	6 (20)	
Pyrexia	7 (19)	6 (20)	5 (56)
Diarrhea	6 (17)	5 (17)	6 (67)
Oropharyngeal pain	6 (17)	1 (3)	
Upper respiratory tract infection	6 (17)	6 (20)	2 (22)
Epistaxis	4 (11)	6 (20)	
Nasopharyngitis	4 (11)	3 (10)	3 (33)
Vomiting			6 (67)
Teething			2 (22)
Dehydration			2 (22)
Metabolic acidosis			2 (22)
Dermatitis diaper			3 (33)
Rash			2 (22)
Urticaria			3 (33)
Eczema			2 (22)
Rhinitis			5 (56)
Catheter-site infection			3 (33)
Device-related infection			3 (33)
Ear infection viral			2 (22)
Bronchiolitis			2 (22)
Varicella			2 (22)
Viral infection			2 (22)
Pyrexia			5 (56)
Hyperthermia			2 (22)
Anemia			4 (44)
Tachycardia			2 (22)
Bradycardia			2 (22)
Cough			3 (33)
Rhinorrhea			2 (22)
Pallor			2 (22)
Hydrocele			2 (22)
SAEs			
Patients with > 0 SAEs, N (%)	2 (6)	1 (3)	[redacted]
WDAEs, N (%)	1 (3)	0	0
Number of deaths, N (%)	0	0	3 (33)
Notable harms, N (%)			

	ARISE		VITAL
AEs	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Sebelipase Alfa (N = 9)
Infusion-associated reactions	2 (6)	4 (13)	[redacted]
Anaphylaxis	0	0	[redacted]
ADA positive	5/35 (14)	0	[redacted]
Chest discomfort	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]
Headache	10 (28)	6 (20)	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]

AE = adverse event; ADA = anti-drug antibodies; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 10%.

Source: ARISE CSR;[22] VITAL CSR.[9]

Discussion

Summary of Available Evidence

Two trials, ARISE and VITAL, met the inclusion criteria for this review. The VITAL trial was a phase II/III, multi-centre, open-label, single-arm study of sebelipase alfa in nine patients with LAL deficiency with growth failure or other evidence of rapidly progressive disease prior to six months of age. The age range at study entry was 1 month to 6 months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Based on the clinical response, dose escalation to 3 mg/kg once weekly could be considered after receiving at least four infusions at a dose of 1 mg/kg once weekly. A further dose escalation to 5 mg/kg once weekly was allowed. The primary objective of the VITAL trial was to evaluate the effect of sebelipase alfa therapy on survival at 12 months of age.

The ARISE trial was a phase III, randomized, multi-centre, double-blind, placebo-controlled study in 66 children and adults with LAL deficiency. Patients were randomized to receive sebelipase alfa at a dose of 1 mg/kg (n = 36) or placebo (n = 30) once every other week for 20 weeks in the double-blind period. The age range at randomization was 4 years to 58 years old. The ARISE trial evaluated improvements in multiple disease-related abnormalities in children and adults. ALT normalization was selected as the primary end point.

Key limitations in both trials were the small sample size and the lack of long-term follow-up. In addition in the ARISE trial, surrogate outcomes were used instead of hard clinical outcomes, and in the VITAL trial, a historical control for the primary outcome was used.

Interpretation of Results

Efficacy

The clinical expert consulted by CADTH indicated that the key efficacy outcomes in ARISE should have been clinical outcomes, such as mortality and morbidity, and not surrogate outcomes. Slowing the progression of liver disease and hence delaying or avoiding liver

transplant is an important outcome for patients with LAL deficiency. Likewise, reducing the risk of extrahepatic morbidity, such as cardiovascular events, is an important treatment goal in patients with LAL deficiency. However, the design of ARISE, with a focus on biochemical markers as surrogate outcomes, was not long enough to evaluate these important clinical outcomes. No deaths occurred during the double-blind period in the ARISE trial, however, as mentioned, the double-blind period was short and there is no evidence to address long-term and key clinical end points such as the need for liver transplant, cardiovascular events, and death. In the VITAL trial, the percentage of patients in the PES surviving to 12 months of age was 67% (6 of 9 patients), with an exact 95% CI for survival of 29.93% to 92.51%. As of May 2017, five patients have survived beyond four years of age and continue to receive sebelipase alfa. The median age (range) at last exposure in the study was 4 years and 7 months (4 years and 2 months to 6 years and 5 months). The median time in the study was 4 years and 1 month. All five patients are living at home and, according to the manufacturer's reports, are making normal social and developmental progress. [redacted] However in the VITAL trial there is no evidence to address long-term survival in these patients, and other key clinical end points such as the need for liver transplant, cardiovascular events, and HRQoL were not assessed.

To assess the effects of sebelipase alfa on survival, the results from VITAL were compared with data from a separate multi-centre, multinational, retrospective natural history study of patients presenting with LAL deficiency before two years of age and diagnosed with LAL deficiency from January 1, 1985 to September 30, 2011 (study LAL-1-NH01). In this cohort, survival was evaluated for a total of 35 patients who presented with LAL deficiency in infancy. A subpopulation of 21 infants who had growth failure within the first six months of life based on criteria similar to those used in the VITAL trial and, like the patients in the VITAL trial, had not received prior HSCT or liver transplant. In this subpopulation of untreated infants with early growth failure, none of the 21 infants survived beyond eight months of age, and the percentage (exact 95% CI) of patients surviving to 12 months of age, determined using the same methodology as in the VITAL trial, was 0% [redacted]. Compared with this historical control, sebelipase alfa treatment appears to provide improvement in survival in infants with LAL deficiency. The design and lack of statistical comparisons with a control group make it difficult to estimate the magnitude of the relative treatment effect. There is uncertainty as to how similar the patients were between VITAL and the LAL-1-NH01 historical cohort. Especially considering the time periods within which both studies occurred, there is potential that observed survival benefits with sebelipase alfa are the result of factors other than a true effect of sebelipase alfa. Comparisons between the VITAL trial and the historical control group do not provide results that are as robust or reliable as those from comparisons within a randomized controlled study. However, due to the rarity of LAL deficiency, which is fatal at an early age with no alternative treatments, it is likely that the single-arm design of VITAL was ethical. In discussion with the clinical expert involved in the review, it was determined that despite the important limitations with the data and non-statistical comparisons, there is a low probability that survival benefits observed in VITAL were influenced to a clinically meaningful degree by differences in diagnosis and supportive treatments (e.g., dietary restriction and LLMs) as compared with the historical cohort. No survival data were available from ARISE.

From the patient group input received by CDR on this submission, it is clear that patients consider improved quality of life and reduction in pain to be important outcomes of treatment. The VITAL trial did not assess HRQoL. The ARISE trial assessed HRQoL using

the FACIT-F, CLDQ, and PedsQL. [redacted]

In the VITAL trial, growth deceleration from birth was observed for all eight patients with available weight data when assessed at study baseline. Improvements in growth from study baseline were observed for all six surviving patients. WFA percentile, a key parameter of growth evaluation in infants, improved significantly for all patients from baseline through the last assessment prior to data cut-off for the CSR provided by the manufacturer (June 10, 2014). Data for other growth parameters such as LFA supported the trends observed for WFA. [redacted]

In the ARISE trial, although the primary efficacy outcome measure, which was the proportion of patients who achieved ALT normalization, was met, only 31% in the sebelipase alfa group achieved normalization in ALT versus 7% in the placebo group by the last time point in the double-blind period. This means that 69% of patients in the sebelipase alfa group did not achieve normalization in ALT after 20 weeks of treatment, indicating a variation in response between patients. Similarly, for the key secondary end point of the proportion of patients who achieved AST normalization, only 42% of patients in the sebelipase alfa group achieved normalization in AST versus 3% in the placebo group by the last time point in the double-blind period. In addition, while the results were statistically significant in favour of sebelipase alfa when compared with placebo for LDL reduction, non-HDL-C reduction, TG reduction, HDL-C increase, and liver fat content reduction, there were some patients who were treated with sebelipase alfa and who had LDL, non-HDL-C, TG, and liver fat content increase, and some patients had their HDL-C decrease, indicating that sebelipase alfa was not effective in reducing lipid levels, liver enzymes, and liver fat content in all treated patients.

Findings from the analyses of the primary and secondary end points of the ARISE trial [redacted] Given the small numbers of patients in each age category, a definitive conclusion regarding the effect of sebelipase alfa on ALT normalization or other end points by age cannot be made. The ARISE trial did not include patients aged 65 years and older. It is not known whether patients aged 65 years and older would respond differently than younger patients. [redacted] although the number of patients in each genetic mutation category was very small. [redacted]

[redacted]

In both trials, sebelipase alfa reduced lipid levels, liver enzymes, and liver fat content (assessed in the ARISE trial only), however, it is unclear how these surrogate outcomes relate to key clinical outcomes in this population. In particular, it is uncertain if sebelipase alfa delayed or stopped progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, or cardiovascular events. While the VITAL trial had treatment for up to four years, this is only a fraction of the expected lifelong treatment people in clinical practice would receive. Hence, the long-term safety and efficacy profile of sebelipase alfa is uncertain. On the other hand, the FDA indicated that "*LDL-C is a well-established risk factor for coronary heart disease, and hyperlipidemia and accelerated atherosclerosis are known complications of LAL deficiency*."[18] In the ARISE trial more than half of the patients enrolled had a baseline LDL-C greater than and equal to 190 mg/dL, indicating that they might have a high risk for coronary heart disease, however there was an imbalance in LDL-C levels at baseline with higher values in the placebo group than in the sebelipase alfa group, hence any statistically significant results should be interpreted with caution. In addition to that, not all patients in the sebelipase alfa group had reduced LDL-C levels by week 20. Hence there is uncertainty around the impact of sebelipase alfa on LDL-C levels, and if there is an improvement to be expected, such improvement is only happening in a subgroup of patients.

Sebelipase alfa has a Notice of Compliance with conditions from Health Canada. In the qualifying notice for sebelipase alfa,[30] Health Canada indicated that in order to support a favourable benefit/risk profile of sebelipase alfa in patients with LAL deficiency , the following data are still required:

- *"The long-term prospective clinical outcomes of Kanuma treated infants who survived beyond 12 months.*
- *The long-term prospective clinical outcomes of Kanuma treatment in children and adults with LAL-D including but not limited to progression of liver and cardiovascular diseases and changes in anthropometric assessments (e.g., length/height z scores and weight z scores).*
- *The impact of Kanuma on the liver. The assessments should include liver imaging studies, liver biopsies, liver synthetic function evaluation and provide data on the clinical progression of liver disease (e.g., delay or reversal liver disease or progression to end-stage liver disease [e.g., utilizing the Model for End-Stage Liver Disease score], receipt of liver transplantation, and fatal outcomes).*
- *The impact of improving dyslipidemia on cardiovascular outcomes including incidence rates of non-fatal stroke, myocardial infarction, and cardiovascular death.*
- *The impact of Kanuma on spleen related complications (splenomegaly, anemia).*
- *Additional evaluations for dosing regimens and dosing modification criteria.*
- *Long-term safety of Kanuma including occurrence of serious hypersensitivity reactions (e.g., anaphylaxis), immunogenicity, and data on neutralizing antibodies."*

Therefore, a key point is that the long-term safety and efficacy of sebelipase alfa is uncertain.

In the open-label extension period of the ARISE trial (Appendix 6), it appeared that ALT and AST normalization were sustained at week 36, along with continued improvements in LDL-C, HDL-C, non-HDL-C, and TG; however, the number of patients contributing to these

outcomes was small ([redacted]), and due to the limitations inherent to the ARISE extension period (open-label nature of the study, the lack of a proper control group, and the lack of power necessary to perform meaningful statistics), no definitive conclusions can be made regarding the long-term treatment effect of sebelipase alfa 1 mg/kg.

[redacted][7].[redacted][22].[redacted]

[redacted] (Appendix 7). [redacted]

Harms

In the VITAL trial, three patients died due to complications related to disease progression (hepatic failure or cardiac arrest) or a non-study-related procedure (peritoneal hemorrhage following abdominal paracentesis). These patients died after receiving between one and four infusions of sebelipase alfa. TEAEs have been reported for all nine (100%) patients. The most frequently reported TEAEs were vomiting, diarrhea, pyrexia, rhinitis, anemia, cough, catheter-site infection, device-related infection, dermatitis diaper, nasopharyngitis, urticaria, tachycardia, rash, chills, and decreased appetite. One patient experienced four study drug-related SAEs, which were characterized as IARs. These serious IARs included grade 3 tachycardia and pallor and grade 2 chills and pyrexia, occurred at a single infusion on week 12 (3 mg/kg once weekly), and resolved the same day following infusion interruption and administration of antihistamine, antipyretic, and IV saline. Other SAEs reported in this study were considered by investigators to be unrelated to sebelipase alfa, and likely represented comorbidities and complications of LAL deficiency. Anaphylaxis was not reported in any patient treated with sebelipase alfa in this study. IARs have been reported for four patients, most commonly pyrexia, vomiting, tachycardia, and chills, and have been predominantly mild and non-serious. No patient has discontinued treatment due to IARs or other study drug-related TEAEs, and no patient has had a permanent dose reduction due to poor tolerability. One patient was discontinued from treatment following a non-study drug-related TEAE of bradycardia, and died of hepatic failure prior to the next scheduled infusion. Four patients have had a dose modification (interruption or decrease) during one or more study infusions due to a TEAE. There is evidence of ADA formation in four of the seven patients who have been tested. Anti-drug antibody positivity was confirmed as early as weeks 5 and 8 (3 patients), and the fourth patient became positive at week 59. Three patients have persistent ADA positivity (> 1 assessment).

In the ARISE trial, there were no deaths. The incidence of SAEs in the double-blind period of the study was low (two patients in the sebelipase alfa group and one patient in the placebo group). Compared with placebo, sebelipase alfa was associated with a lower

incidence of TEAEs (86% versus 93%, respectively). Overall, the most common (i.e., incidence > 10%) TEAEs reported among the 36 patients in the sebelipase alfa group were headache (28%), pyrexia (19%), diarrhea, oropharyngeal pain, and upper respiratory infection (each 17%), and epistaxis and nasopharyngitis (each 11%). Of these events, the only events occurring with at least 5% higher incidence in the sebelipase alfa group than in the placebo group were headache (28% versus 20%) and oropharyngeal pain (17% versus 3%, respectively). IARs were reported in both sebelipase alfa and placebo-treated patients with a higher proportion of patients in the placebo arm had events classified as IARs. During the double-blind period, two (6%) of 36 patients in the sebelipase alfa group experienced a total of 10 IARs, and four (13%) of 30 patients in the placebo group experienced a total of five IARs. Given the very low frequency of IARs in both the SA and placebo groups, it is not possible to draw any conclusions on the clinical features of IARs due to sebelipase alfa administration from this study. Anaphylaxis was not reported in any patient treated with sebelipase alfa in this study. A total of 14.3% of patients in the sebelipase alfa group had at least one positive ADA test during the double-blind period, and only 5.7% were positive at multiple time points during the double-blind period. In the open-label (OL) extension period of the ARISE trial no new safety signals were apparent, with 96% of patients experiencing at least one AE (the most common of which were headache, diarrhea, and pyrexia) and 6% experiencing a SAEs. In addition, five patients (14%) were positive for antibodies in the extension analysis set. However, due to the limitations inherent to the ARISE extension period (open-label nature of the study, and the lack of a proper control group), no definitive conclusions could be made regarding the long-term treatment safety of sebelipase alfa 1mg/kg.

Potential Place in Therapy[2]

There are two distinct clinical presentations of LAL deficiency: the rapidly progressing infant-onset type (previously Wolman disease) and the later onset type in children and adults (previously CESD). Both types are associated with hepatic and extrahepatic morbidity and mortality.

The rapidly progressive type of LAL deficiency that presents in infancy (i.e., the sebelipase alfa VITAL trial population) is associated with complete loss of LAL enzyme function caused by mutations in the LIPA gene, resulting in 100% mortality before one year of age. Diagnosis of this type of LAL deficiency in Canada is typically made within the first two to six months of life, based on clinical (e.g., early growth restriction), biochemical, LAL enzyme activity assays, and LIPA gene analysis. It is at the moment not part of newborn screening programs.

The other form of LAL deficiency in children and adults (i.e., the sebelipase alfa ARISE trial population) has a poorly defined clinical course because of substantial variability in clinical phenotype characterized by a much wider variation in LAL enzyme activity, as compared with the infant form, in that enzyme activity may range from being decreased to completely absent. Age of presentation may be as late as the sixth decade of life. Consequently, this form is more difficult to diagnose and these patients likely are underdiagnosed in Canada and elsewhere. In addition to clinical, biochemical, and enzyme activity assessments, diagnosis also typically requires liver biopsy (evidence of microvesicular steatosis and cirrhosis), and sophisticated histological and immunohistochemical analyses to help differentiate from non-alcoholic fatty liver disease. The key clinical concerns in this

2 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

subpopulation are liver cell failure progressing to cirrhosis, and hyperlipidemia and resultant risk of early atherosclerotic cardiovascular disease and/or stroke, and premature death.

The clinical expert consulted by CADTH noted that there is an unmet need for an effective and safe treatment that alters the natural history of LAL deficiency. Prior to sebelipase alfa, treatment for both types of LAL deficiency was limited to LLMs, HSCT and bone marrow transplantation, and liver transplantation. However, there is limited or no evidence that these treatments delay progression or modify the risk of death in a significant way in patients with LAL deficiency. As well, these treatments may be associated with increased morbidity and mortality. For example, HSCT and bone marrow transplantation are not used routinely for either group of LAL deficiency patients because of high mortality rates (> 70%).

Based on the data reviewed from the VITAL trial, sebelipase alfa appears to impact mortality in the infantile-onset form of LAL deficiency. These patients should be initiated with treatment after diagnosis is established by clinical, biochemical, LIPA gene analysis, and lysosomal activity assays. Monitoring of treatment and outcomes will be necessary and should be done at centres with access to specialists in the care of patients with LAL deficiency, including a multidisciplinary team of providers in pediatric cardiology, gastroenterology, surgery, genetics, pathology, nutrition, and developmental follow-up.

The design and duration of the ARISE trial, particularly the focus on surrogate outcomes as opposed to key clinical end points (need for liver transplant, atherosclerotic cardiovascular disease, and death), as well as the heterogeneity of the disease and progression of the late-onset form, makes it difficult to decide in which patients sebelipase alfa may be of benefit and what is the optimal dose for the individual patient. LAL enzyme assays of significantly decreased LAL activity, progression of liver disease as assessed by hepatomegaly, liver biopsy, and growth failure in children, are factors which may be considered by clinicians in considering sebelipase alfa use. There is a need for greater clarity regarding time of initiation, and need for continued gathering of data in order to better understand the correspondence between improvements in surrogate markers and relevant long-term end points. If treated with sebelipase alfa, children and adults would also require close management from a multidisciplinary care team with experience managing these patients.

Conclusions

Two trials, ARISE and VITAL, met the inclusion criteria for this review. While sebelipase alfa seemed to improve growth, biochemical markers, and survival in patients presenting with LAL deficiency in infancy in the VITAL trial, with 67% of sebelipase alfa-treated patients surviving to 12 months of age, there is uncertainty regarding the long-term efficacy of sebelipase alfa in continuing to improve survival for infants who survive to 12 months. In the ARISE trial, sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in some children and adults with LAL deficiency. However, it is uncertain if sebelipase alfa delayed or stopped important LAL deficiency-related morbidities, including progression to cirrhosis, hepatocellular carcinoma, need for liver transplant, or cardiovascular events in the non-infant population. Survival could not be evaluated in ARISE. Also, there was no improvement in HRQoL as compared with placebo. The safety profile of sebelipase alfa was similar to placebo in the controlled phase of the trials except for ADA formation. While there were no apparent differences in safety results for sebelipase alfa between the controlled phase of the studies and the open-label extension, conclusions regarding the long-term safety of sebelipase alfa in patients with LAL deficiency are limited, due to the absence of a comparator arm and the short duration of treatment.

Appendix 1: Patient Input Summary

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Two groups submitted patient input for the review of Kanuma.

The Canadian Liver Foundation (CLF) is a national health charity dedicated to supporting awareness, education, and research for all forms of liver disease. CLF has received unrestricted educational grants from Alexion Pharma Canada Corp in the last two years.

The Isaac Foundation is a patient group that provides support, guidance, and education for families of individuals suffering from rare disorders. They have not received funding from anyone in the past two years.

Neither CLF nor the Isaac Foundation declared any conflicts of interest with regard to their submissions.

2. Condition-Related Information

Information describing the patient and family perspectives was ascertained using an online questionnaire open to patients, caregivers, and professionals from across Canada (open from October 20 to November 13, 2017) using CLF social media channels and the CLF website, along with specific contact lists. In addition, another online survey was utilized to obtain responses from Canadian and international patients. Information was also obtained through one-on-one interviews with patients using current therapy, parents of patients on current therapy, and with both patients and caregivers hoping to gain access to therapy. Due to the fact that lysosomal acid lipase (LAL) deficiency is an ultra-rare disease in Canada, there were expectedly few respondents to the surveys.

LAL deficiency is an ultra-rare, genetic, chronic, and progressive disease whereby the enzyme responsible for cholesterol ester and triglyceride metabolism is deficient or absent, leading to harmful lipid buildup in the lysosomes. LAL deficiency is predominantly a pediatric condition, with a large number of patients being diagnosed as infants, but is also diagnosed in older children and adults. The very low or absent levels of the LAL enzyme lead to severe and early-onset LAL deficiency in infants (also known as Wolman disease) and is characterized by a failure to grow, difficulties in absorbing nutrients from food (malabsorption), persistent vomiting and diarrhea, swollen belly, and jaundice. Other signs (altered biochemical levels such as elevated ALT and bilirubin) are not commonly visible except when investigated using blood tests. The median age of death for patients with early-onset LAL deficiency is under four months of age, while survival beyond one year is typically rare. Late-onset LAL deficiency in children and adults is termed cholesteryl ester storage disease (CESD) and is characterized by a buildup of fat in the liver, spleen, and other organs. As the liver damage progresses, patients may experience ascites (fluid buildup in the abdomen), easy bleeding or bruising, and jaundice. Patients can also experience esophageal varices, microvesicular or mixed hepatic steatosis, fibrosis, and cirrhosis. In addition, patients also experience gastrointestinal symptoms and cardiovascular complications (such as stroke and coronary artery disease) that can arise from the buildup of lipids in the blood.

Patients with LAL deficiency experience life-altering impacts of the disease on their day-to-day lives and on their quality of life; including on their physical health, school and everyday life (especially missed days of school), and on their mental well-being. Specific symptoms

include constant pains (including abdominal pain), enlarging liver and spleen, headaches, bouts of extreme fatigue, getting sick easily and having it last a long time, itching, and skin lesions and scarring. As one patient stated, “My liver aches, feels large and is uncomfortable. I feel lethargic. My wife and I have a 1-year-old daughter so naturally I have a feeling of despair because of my concern for my family if I were to make an early departure.” Later in the disease patients also experience more severe symptoms, including liver cirrhosis, neurodegeneration, liver failure (followed by liver transplantation if they survive), and early death.

The day-to-day activities and quality of life of caregivers is also highly impacted, as they often experience stress, they are emotionally drained, and they are constantly worried. Work is often negatively impacted due to the need for constant patient care and the continual medical appointments. In addition, due to the rarity of this disease, caregivers often lack support systems that are normally available to others experiencing or caring for patients with more frequently observed diseases. As one caregiver stated, “As a caregiver, it affects my life by interfering with my job, my stress levels, and overall consumes my time. I have to plan medical tests, treatments, follow ups around my work schedule, my kid’s school schedule, and sport schedule. I have to take the time to research treatments, symptoms, medical tests, and financial medical support. With LAL deficiency being such a rare disease there is no support group to attend, so I must seek others through social media, and try to reach others through our story. But the hardest thing of all as a caregiver, is knowing that your child (in my case all four children) has a rare disease and having them poked, tested, and studied. I know in heart the testing needs to be done, because it helps the doctors understand the disease. Hearing "we just don't know" is the hardest answer to accept.” In addition to the aforementioned, families are devastated if they lose a child to the early-onset, severe, infant form of LAL deficiency.

3. Current Therapy Related Information

Due to the similarity of some of the early signs and symptoms of LAL deficiency to other, more common diseases, it can often be months or even years for patients to be properly diagnosed. The definitive diagnosis is made with a blood spot test which measures the activity levels of the LAL enzyme.

The current standard of care for patients with LAL deficiency includes management strategies such as providing infants with nutritional supplements and following a strict diet that is low in cholesterol and saturated fats for children and adults. However, even with these management strategies, there is limited impact and no observed benefit on morbidity or mortality rates. Statins have also been used in both children and adults; however, there is no benefit of their use in slowing the progression of liver disease. In addition, other lipid-lowering medications have also been used with little to no benefit. Side effects from the aforementioned medications include muscle pain and damage, drowsiness and dizziness, vomiting, headaches, difficulty sleeping, memory loss, mental confusion, high blood sugars, and, in severe cases, kidney damage or failure. Stem cell therapy has been used and, while it has been noted to be successful in restoring normal LAL activity in some patients, it is extremely risky. Liver transplantation is another option for patients; however, it is not a viable long-term solution as the donated organ is still at risk of developing liver disease due to the continual LAL enzyme deficiency. In addition, there are numerous side effects from liver transplantation including bile duct complications, blood clots, transplant rejection or failure of the donated liver, and mental confusion or seizures.

Due to the life-threatening aspect of LAL deficiency in infants through adulthood, there is a need for a therapy that addresses the underlying enzyme deficiency, instead of treating the symptoms of the disease.

4. Expectations About the Drug Being Reviewed

Of those patients surveyed, all had high hopes that sebelipase alfa would not only help treat their disease but also be easily available to them. Families believe that sebelipase alfa will have a dramatically positive effect on both the patient and the caregiver, with an increased chance at a longer life being the main consideration. They see how well the clinical trial and its extension went, how well sebelipase alfa has worked in patients receiving it both internationally and in Canada through compassionate use requests, and how it has been rapidly approved in other countries and hope that the same will happen in Canada. As one medical professional stated, “There are no good treatments readily available for this disorder. We need more options.”

Of those patients who have received sebelipase alfa, children and adults patients with LAL deficiency have seen reductions in ALT liver enzymes and decreased liver fat content. Regression of the disease and its life-threatening symptoms (decrease in size of internal organs, lower liver enzyme levels) were noted by every respondent of the survey and there were no adverse events reported. In addition, muscle and joint pain disappeared, stomach pain and headaches were reduced, and stress levels for parents/caregivers were reduced. As one parent stated, “My boys have had no side effects from the Kanuma. They get to live basically a normal life now and have hope for a future! I can be relieved that I don't have to fear watching my children die!” This treatment is observed as life-saving therapy to both patients and their caregivers.

While caregivers noted that sebelipase alfa is not a long-term cure for LAL deficiency in infants, there was evidence of significant survival benefit with 67% of infants surviving beyond one year. This provides hope to parents of infants affected by LAL deficiency.

Of the few disadvantages that were noted, scheduling work and activities around the bi-weekly infusions (including travel time) were the most prevalent, along with the fear that this medication would not be available to all patients with LAL deficiency.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 29, 2017
Alerts:	Bi-Weekly search updates until April 11, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Kanuma or (sebelipase adj2 alfa) or (SBC adj2 "102") or SBC102 or (lipase adj2 A) or (lysosomal adj2 acid adj2 lipase) or K4YTU42T8G or 1276027-63-4).ti,ab,ot,kf,hw,rn,nm.
2	Wolman Disease/ or Cholesterol Ester Storage Disease/ or Dyslipidemias/ or Enzyme Replacement Therapy/
3	((Wolman* adj2 disease) or (acid adj2 lipase adj2 deficienc*) or (acid adj2 lipase adj2 disease*) or (Wolman* adj2 xanthomatosis) or (Familial adj2 xanthomatosis) or (cholesterol adj2 esters) or (cholesteryl adj2 esters) or (cholesterol adj2 ester adj2 deficiency) or (cholesteryl adj2 ester adj2 deficiency) or (cholesterol adj2 ester adj2 disease) or (cholesteryl adj2 ester adj2 disease) or (cholesterol adj2 ester adj2 storage adj2 disease) or (cholesteryl adj2 ester adj2 storage adj2 disease) or (acid adj2 cholesterol adj2 ester adj2 hydrolase adj2 deficienc*) or (acid adj2 cholesteryl adj2 ester adj2 hydrolase adj2 deficienc*) or (lysosomal adj2 acid adj2 lipase adj2 deficienc*) or (lysosomal adj2 acid adj2 lipase adj2 disease) or (LCAT adj2 deficienc*) or (enzyme adj2 replacement adj2 therapy) or (enzyme adj2 therap*) or (LAL adj2 deficienc*) or LAL-D or dyslipidemia* or (LIPA adj2 deficienc*) or dyslipoproteinemia or (mckusick adj2 "27800")).ti,ab,ot,kf,hw.
4	2 or 3
5	1 and 4
6	5 use medall
7	*sebelipase alfa/
8	(Kanuma or (sebelipase adj2 alfa) or (SBC adj2 "102") or SBC102 or (lipase adj2 A) or (lysosomal adj2 acid adj2 lipase)).ti,ab,ot,kw.
9	7 or 8
10	Wolman disease/ or cholesterol ester storage disease/ or dyslipidemia/ or enzyme replacement/ or enzyme deficiency/
11	((Wolman* adj2 disease) or (acid adj2 lipase adj2 deficienc*) or (Wolman* adj2 xanthomatosis) or (Familial adj2 xanthomatosis) or (cholesterol adj2 esters) or (cholesteryl adj2 esters) or (cholesterol adj2 ester adj2 deficienc*) or (cholesteryl adj2 ester adj2 deficienc*) or (cholesterol adj2 ester adj2 disease) or (cholesteryl adj2 ester adj2 disease) or (cholesterol adj2 ester adj2 storage adj2 disease) or (cholesteryl adj2 ester adj2 storage adj2 disease) or (acid adj2 cholesterol adj2 ester adj2 hydrolase adj2 deficienc*) or (acid adj2 cholesteryl adj2 ester adj2 hydrolase adj2 deficienc*) or (lysosomal adj2 acid adj2 lipase adj2 deficienc*) or (lysosomal adj2 acid adj2 lipase adj2 disease) or (LCAT adj2 deficienc*) or (enzyme adj2 replacement adj2 therapy) or (enzyme adj2 therap*) or (LAL adj2 deficienc*) or LAL-D or dyslipidemia* or (LIPA adj2 deficienc*) or dyslipoproteinemia or (mckusick adj2 "27800")).ti,ab,ot,kw.
12	10 or 11
13	9 and 12
14	13 use oemezd
15	conference abstract.pt.
16	6 or 14
17	16 not 15
18	exp animals/
19	exp animal experimentation/ or exp animal experiment/
20	exp models animal/
21	nonhuman/
22	exp vertebrate/ or exp vertebrates/

MULTI-DATABASE STRATEGY	
#	**Searches**
23	or/18-22
24	exp humans/
25	exp human experimentation/ or exp human experiment/
26	or/24-25
27	23 not 26
28	17 not 27
29	(comment or newspaper article or editorial or letter or note).pt.
30	28 not 29
31	remove duplicates from 30

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	November 23 to November 27, 2017
Keywords:	Kanuma (sebelipase alfa), lysosomal acid lipase (LAL) deficiency
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Su K, Donaldson E, Sharma R. Novel treatment options for lysosomal acid lipase deficiency: Critical appraisal of sebelipase alfa. Application of Clinical Genetics [Internet]. 2016 [cited 2017 Dec 20];9:157-67. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5074735/pdf/tacg-9-157.pdf	Review
Schonfeld EA, Brown RS, Jr. Genetic Testing in Liver Disease: What to Order, in Whom, and When. Clin Liver Dis. 2017 Nov;21(4):673-86.	Review
Weiskirchen R. Fast progression of liver damage in lysosomal acid lipase deficiency. Curr Med Res Opin. 2017 Nov;33(11):2081-3.	Review
Erwin AL. The role of sebelipase alfa in the treatment of lysosomal acid lipase deficiency. Therap adv in gastroenterol [Internet]. 2017 Jul [cited 2017 Dec 20];10(7):553-62. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5484437/pdf/10.1177_1756283X17705775.pdf	Review
Camarena C, Aldamiz-Echevarria LJ, Polo B, Barba Romero MA, Garcia I, Cebolla JJ, et al. Update on lysosomal acid lipase deficiency: Diagnosis, treatment and patient management. Med Clin (Barc). 2017 May 10;148(9):429.	Review
Paton DM. Sebelipase alfa: enzymatic replacement treatment for lysosomal acid lipase deficiency. Drugs Today (Barc). 2016 May;52(5):287-93.	Review
Woodard TJ, Kim C, Calderon F, Panjwani Q. Managing lysosomal acid lipase deficiency. U S Pharmcist [Internet]. 2017 [cited 2017 Dec 21];(5):HS. Available from: https://www.uspharmacist.com/article/managing-lysosomal-acid-lipase-deficiency	Review
Jurecka A, Opoka-Winiarska V, Lugowska A, Tylki-Szymanska A. Wolman disease. Pediatria Polska. 2013;88(1):64-8.	Review
Balwani M, Breen C, Enns GM, Deegan PB, Honzik T, Jones S, et al. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. Hepatology. 2013 Sep;58(3):950-7.	Phase I/II non-pivotal trial
Valayannopoulos V, Malinova V, Honzik T, Balwani M, Breen C, Deegan PB, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. J Hepatol. 2014 Nov;61(5):1135-42.	Non-randomized study
Fasano T, Pisciotta L, Bocchi L, Guardamagna O, Assandro P, Rabacchi C, et al. Lysosomal lipase deficiency: Molecular characterization of eleven patients with Wolman or cholesteryl ester storage disease. Mol Genet Metab. 2012 Mar;105(3):450-6.	Non-randomized study

Appendix 4: Detailed Outcome Data

Table 16: ALT Observed Values and Changes from Baseline (PES) for the VITAL Trial

	Observed Value			Change from Baseline[a]		
	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)
Baseline[a]	9	130.11 (95.51)	145.00 (16.0 to 297.0)	NA	NA	NA
Week 2	5	95.00 (90.92)	45.00 (21.0 to 241.0)	5	−60.0 (84.30)	−23.00 (−171.0 to 15.0)
Week 4 (Month 1)	5	34.00 (22.78)	31.00 (14.0 to 71.0)	5	−85.80 (92.95)	−33.00 (−226.0 to −4.0)
Week 12 (Month 3)	5	28.20 (10.62)	27.00 (15.0 to 44.0)	5	−91.60 (113.64)	−24.00 (−273.0 to −4.0)
Week 24 (Month 6)	5	44.20 (28.75)	39.00 (15.0 to 90.0)	5	−65.20 (101.11)	−11.00 (−207.0 to 34.0)
Week 48 (Month 12)	4	28.50 (0.58)	28.50 (28.0 to 29.0)	4	−34.00 (59.55)	−13.50 (−121.0 to 12.0)
Week 60 (Month 15)	4	34.25 (5.74)	33.00 (29.0 to 42.0)	4	−28.25 (62.85)	−10.50 (−118.0 to 26.0)

ALT = alanine aminotransferase; NA = not available; PES = primary efficacy analysis set; SD = standard deviation.
[a] Baseline was defined as the last measurement prior to the first infusion of sebelipase alfa.
Source: VITAL CSR.[9]

Table 17: AST Observed Values and Changes from Baseline (PES) for the VITAL Trial

	Observed Value			Change from Baseline[a]		
	n	Mean (SD)	Median (range)	n	Mean (SD)	Median (range)
Baseline[a]	9	293.78 (256.06)	125.00 (71.0 to 716.0)	NA	NA	NA
Week 2	4	123.50 (112.63)	77.00 (49.0 to 291.0)	4	−91.50 (109.00)	−42.50 (−256.0 to −25.0)
Week 4 (Month 1)	4	69.75 (36.95)	62.00 (35.0 to 120.0)	4	−139.50 (192.42)	−55.50 (−427.0 to −20.0)
Week 12 (Month 3)	5	50.20 (18.13)	44.00 (33.0 to 75.0)	5	−136.00 (188.39)	−61.00 (−472.0 to −27.0)
Week 24 (Month 6)	5	62.60 (32.89)	56.00 (28.0 to 106.0)	5	−113.60 (185.84)	−57.00 (−441.0 to 15.0)
Week 48 (Month 12)	4	39.00 (5.72)	39.50 (32.0 to 45.0)	4	−44.50 (14.23)	−43.50 (−62.0 to −29.0)
Week 60 (Month 15)	4	45.25 (9.54)	43.00 (37.0 to 58.0)	4	−38.25 (18.89)	−41.50 (−57.0 to −13.0)

AST = aspartate aminotransferase; NA = not available; PES = primary efficacy analysis set; SD = standard deviation.
[a] Baseline was defined as the last measurement prior to the first infusion of sebelipase alfa.
Source: VITAL CSR.[9]

Table 18: ALT Normalization, LDL-C Reduction, Non-HDL-C Reduction, AST Normalization, TG Reduction, HDL-C Increase, and Liver Fat Content Reduction in the ARISE Trial (FAS, DB Treatment Period)

	ARISE	
	Sebelipase Alfa (N = 36)	**Placebo (N = 30)**
ALT normalization [n (%)][a]		
N	36	30
Yes	11 (31)	2 (7)
Difference	24%	
P value[b]	0.0271	
LDL-C reduction (percentage change from baseline)		
N	36	30
Mean (SD)	−28.42 (22.304)	−6.25 (13.015)
Median (range)	[redacted]	[redacted]
Difference	[redacted]	
P value[b]	< 0.0001	
Non-HDL-C reduction (percentage change from baseline)		
N	36	30
Mean (SD)	−27.97 (18.612)	–6.94 (10.922)
Median (range)	[redacted]	[redacted]
Difference	[redacted]	
P value[b]	< 0.0001	
AST normalization [n (%)][a]		
N	36	29
Yes	15 (42)	1 (3)
Difference	[redacted]	
P value[b]	0.0003	
TG reduction (percentage change from baseline)		
N	36	30
Mean (SD)	−25.45 (29.411)	−11.14 (28.827)
Median (range)	[redacted]	[redacted]
Difference	[redacted]	
P value[b]	0.0375	
HDL-C increase (percentage change from baseline)		
N	36	30
Mean (SD)	19.57 (16.833)	−0.29 (12.360)
Median (range)	[redacted]	[redacted]
Difference	[redacted]	
P value[b]	< 0.0001	
Liver fat content reduction (percentage change from baseline)		
N	32	25
Mean (SD)	−31.98 (26.763)	−4.21 (15.559)

	ARISE	
	Sebelipase Alfa (N = 36)	**Placebo (N = 30)**
Median (range)	[redacted]	[redacted]
Difference	[redacted]	
P value[b]	< 0.0001	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double blind; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; TG = triglycerides.
[a] Abnormal ALT/AST values at baseline which became normal (below the age- and gender-specific upper limit of normal [ULN]) at the end of the DB treatment period. If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the patient was not considered to have ALT normalization in the analysis. Patients with normal AST values at baseline were excluded from analysis of AST normalization end point. Abnormal baseline ALT/AST was defined as exceeding the ULN from the central laboratory.
[b] Wilcoxon rank sum test for treatment differences.
Source: ARISE CSR.[22]

Table 19: ALT Normalization, LDL-C Reduction, Non-HDL-C Reduction, AST Normalization, TG Reduction, HDL-C Increase, and Liver Fat Content Reduction in the ARISE Trial by Age at Randomization (FAS, DB Treatment Period)

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double blind; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; SD = standard deviation; TG = triglycerides.

[a] Abnormal ALT/AST values at baseline which became normal (below the age- and gender-specific ULN) at the end of the DB treatment period. If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the patient was not considered to have ALT normalization in the analysis. Patients with normal AST values at baseline were excluded from analysis of AST normalization end point. Abnormal baseline ALT/AST were defined as exceeding the ULN from the central laboratory.

[b] Wilcoxon rank sum test for treatment differences.

Source: ARISE CSR.[22]

Table 20: ALT Normalization, LDL-C Reduction, Non-HDL-C Reduction, AST Normalization, TG Reduction, HDL-C Increase, and Liver Fat Content Reduction in the ARISE Trial by Genetic Mutation (FAS, DB Treatment Period)

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double blind; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; SD = standard deviation; TG = triglycerides.
[a] Abnormal ALT/AST values at baseline which became normal (below the age- and gender-specific ULN) at the end of the DB treatment period. If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the patient was not considered to have ALT normalization in the analysis. Patients with normal AST values at baseline were excluded from analysis of AST normalization end point. Abnormal baseline ALT/AST were defined as exceeding the ULN from the central laboratory.
[b] Wilcoxon rank sum test for treatment differences.
Source: ARISE CSR.[22]

Table 21: ALT Normalization, LDL-C Reduction, Non-HDL-C Reduction, AST Normalization, TG Reduction, HDL-C Increase, and Liver Fat Content Reduction in the ARISE Trial by Baseline Fibrosis or Cirrhosis Status (FAS, DB Treatment Period)

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double blind; FAS = full analysis set; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; SD = standard deviation; TG = triglycerides.

[a] Abnormal ALT/AST values at baseline which became normal (below the age- and gender-specific ULN) at the end of the DB treatment period. If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the patient was not considered to have ALT normalization in the analysis. Patients with normal AST values at baseline were excluded from analysis of AST normalization end point. Abnormal baseline ALT/AST were defined as exceeding the ULN from the central laboratory.

[b] Wilcoxon rank sum test for treatment differences.

Source: ARISE CSR.[22]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Chronic Liver Disease Questionnaire (CLDQ)
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)
- Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales

Findings

Table 22: Validity of Outcomes

Instrument	Type	Evidence of Validity	MCID	References
CLDQ	The CLDQ is a HRQoL instrument for patients with chronic liver disease.	Yes	0.5 on a scale between 1 and 7[a] LAL-D: unknown	Younossi et al.[23]
FACIT-F	Assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function.	FACT in cancer patients No evidence for patients with LAL-D	Cancer: 3 to 7 points (range) (FACT-General) RA: 3 to 4 points (range) LAL-D: Unknown	Cella et al. 2005[27] Webster et al. 2003[26]
Peds QL 4.0 Generic Core Scales	• Patient report and parent report (specific for different ages) • 5-point Likert scale for patients ≥ 5 years of age • 3-point Likert scale for patients < 5 years of age, anchored to happy-to-sad faces	Yes	Total Scale Score of the child self-report : 4.4 Total Scale Score for parent proxy-report: 4.5 LAL-D: Unknown	Varni et al. 1999[28] Varni et al. 2001[29] Varni et al. 2002[31] Varni et al. 2003[32]

CLDQ = Chronic Liver Disease Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FACT = Functional Assessment of Cancer Therapy; HRQoL = health-related quality of life; LAL-D = lysosomal acid lipase deficiency; MCID = minimal clinically important difference; PedsQL 4.0 = Pediatric Quality of Life Inventory; RA = rheumatoid arthritis.

[a] Younossi et al.[23] reported that a change of 0.5 on the scale from 1 to 7 would signify an important difference in score; however, there is no indication that this was validated using conventional methods for estimating a MCID.

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is the first disease-specific health-related quality of life (HRQoL) instrument systematically developed to measure longitudinal change over time in patients with chronic liver disease (CLD). A comprehensive, methodological framework consistent with the development of other disease-specific HRQoL instruments was employed in the development of the CLDQ.[23,33] In order to develop the initial questionnaire, the authors incorporated the results of previous studies that examined the impact of CLD on patients' lives and HRQoL, held interviews (personal and telephone) and focus groups with patients suffering from CLD, and ascertained the expert opinions of 20 hepatologists and experts.[23] The final CLDQ includes 29 items in the following six domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.[23,24] A 7-point Likert scale is used to grade the response to each item, in which 1 point indicates the worst and 7 points

the best possible function.[23,24] Each domain score is calculated by dividing the total of the scores for each item in the domain by the number of items in the domain.[23] Higher CLDQ scores indicate less HRQoL impairment.[24]

To ensure the CLDQ was valid, reliable, and responsive, 133 patients who were categorized (using a modified Child-Pugh classification), as having either no cirrhosis, early cirrhosis (Child's A), or advanced cirrhosis (Child's B and C) from a hepatology practice, who were greater than and equal to 18 years of age, had CLD, and who lacked other types of chronic diseases, co-morbid psychiatric or emotional conditions, as well as language or cognitive difficulties, were subsequently included in the initial assessment.[23] These patients were also administered the Medical Outcomes Study Short Form (36) Health Survey (SF-36) at the same visit. Of the 133 patients, the CLDQ showed a gradient between patients without cirrhosis, Child's A cirrhosis, and those with Child's B or C cirrhosis.[23] In addition to the first administration, the CLDQ, SF-36, and Global Rating of Change (which was used to assess whether patients were stable or had changed), were administered after six months in 46 of the 133 original patients.[23] The intraclass correlation of the patients who were classified as stable (n = 15 [33%]) for the overall CLDQ was 0.59. Changes in the overall CLDQ score highly correlated with the Global Rating of Change (r = 0.84, P = 0.02) in patients who had deteriorated over the six-month period. In addition, the fatigue and abdominal symptom domain of the CLDQ were also observed to be highly correlated with the GCR (r = 0.83 and r = 0.90, respectively; P = 0.006). No significant changes in the other CLDQ domains were statistically significant.[23] Changes in the SF-36 were also observed to correlate with changes in the Global Rating of Change, being 0.23 for the mental component score and 0.23 for physical component score (P = 0.57).[23] Therefore, the authors of this main validation study concluded that CLDQ was short, easy to administer, produces both a summary score and domain scores, and correlates with the severity of liver disease.[23] In addition to this initial study,[23] the CLDQ has been widely validated and used.[24,34-37] Also, a direct association has been reported between CLDQ and the EuroQol 5-Dimensions questionnaire (EQ-5D) as well as the SF-36.[23,37]

Younossi et al.[23] reported that a change of 0.5 on the scale from 1 to 7 would signify an important difference in score; however, there is no indication that this was validated using conventional methods for estimating a minimal clinically important difference (MCID).[23] No MCID was identified for patients with LAL-D.

Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) questionnaire

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system is a group of HRQoL questionnaires focused on the management of chronic illness.[26] The original instrument (Functional Assessment of Cancer Therapy [FACT]) was developed and validated in cancer patients.[38] FACIT was later derived from FACT and validated in patients with chronic conditions such as multiple sclerosis and rheumatoid arthritis.[26] FACIT is based on a generic core questionnaire (FACT-General) which includes 27 items divided into four primary domains: physical, social/family, emotional, and functional well-being.[26] The FACIT-F scale (FACIT-F) is a questionnaire that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function. The fatigue subscale has a seven-day recall period and includes 13 items scored using a 4-point Likert scale (subscale score range 0 to 52).[25] Physical, emotional, social, and functional well-being domains, as well as a fatigue subscale (40 items in total), make up the total score, ranging from 0 (worst) to 160 (best).[25,26]

Alternatively, the Trial Outcome Index score may be calculated by summing the physical well-being, functional well-being and fatigue subscales.[26] Although no information on the validity of FACIT-F or its MCID in patients with lysosomal acid lipase (LAL) deficiency was identified, the MCID for the FACT-General total score ranged from 3 points to 7 points in cancer patients, and the MCID in the FACIT-F ranged from 3 points to 4 points in rheumatoid arthritis patients.[26,27]

PedsQL Version 4.0 (PedsQL 4.0) Generic Core Scales

The original PedsQL was developed as an HRQoL measure that addressed the paucity of appropriately validated and reliable instruments incorporating both the child and parental experience with chronic health conditions. The PedsQL uses a modular approach and incorporates both generic and disease/symptom-specific items that are appropriate for the assessment of pediatric chronic conditions.[28] The generic HRQoL measure was developed using pediatric cancer as the model due to the fact that consequences of this chronic condition (rather than specific cancer symptoms) appropriately cross over with many other pediatric chronic health conditions.[28] The PedsQL 4.0 Generic Core Scales are comprised of 23-items under the following modules: Physical Functioning (eight items), Emotional Functioning (five items), Social Functioning (five items), and School Functioning (five items).[29] These Generic Core Scales are comprised of both the parent proxy-report and the child self-report formats that assess health perceptions. The child self-report format is specific for ages five years to seven years, eight years to 12 years, and 13 years to 18 years of age, while the corresponding parent proxy reports are specific for toddlers (ages two to four years, for which there is no child self-assessment report), young children (ages five years to seven years), children (ages eight years to 12 years), and adolescents (ages 13 years to 18 years). The questions ask how much of a problem each item has been in the past month. A 5-point Likert response scale is used across the child reports (from ages eight years to 18 years) and the corresponding parent report, and include the following responses with corresponding scores: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem. In addition, a 3-point scale is used for simplification and ease of use for children who are aged five years to seven years and include: 0 = not at all a problem; 2 = sometimes a problem; and 4 = a lot of a problem, with each of the response choices anchored to a happy-to-sad faces scale.[29] The scores, which are reversed scored, are transformed linearly to a 0 to 100 scale, whereby 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0; with higher scores indicative of a higher HRQoL. In order to account for missing data, the sum of the items divided by the number of items that are answered is computed in order to ascertain the Scale Score. If greater than 50% of the items within the scale are missing, then the Scale Score cannot be obtained. In order to ascertain the Psychosocial Health Summary Score (comprised of 15 items), the sum of the items is divided by the items answered in the School Functioning, Emotional, and Social Subscales.[29] There are currently more than 60 translations of the PedsQL 4.0 Generic Cores Scales that have been validated.[39,40]

In order to validate the PedsQL Generic Core Scales, a sample of chronically ill (as reported by their parents in a specialty clinic [n = 683]), acutely ill (parents reported no presence of chronic illness and attended a specialty clinic [n = 207]), and healthy children (identified at their physician's office during regular visits or using telephone calls [n = 730]) between the ages of two to 18 years were included.[29] Construct validity was ascertained using the known-groups method, whereby scale scores were compared across groups that are known to differ in the specific health constructs being examined (in this case healthy versus acute or healthy versus chronic conditions). In addition, potentially confounding

factors such as age, gender, and ethnicity were also examined across health states. Hypothesizing that healthy children would have a higher HRQoL, Varni et al. noted that the PedsQL differentiated between the different health states (healthy, acute, and chronically ill) and it also correlated with illness burden and morbidity measures.[29] Internal consistency reliabilities generally exceeded the standard alpha coefficients of 0.70. The Total Scale Score across the ages for the self-report and proxy-report were 0.88 and 0.90, respectively, indicating this as an appropriate primary analysis summary score. The Physical Health and Psychosocial Health Summary Scores were >0.8 for the self-report and the proxy-report; hence, the authors determined they were best for secondary analyses. The Emotional, Social, and School Functioning Subscales generally obtained alpha coefficients around 0.70; therefore, the authors suggested these be used for descriptive or exploratory analyses.[29]

Varni et al.[31] then examined three studies in order to determine the sensitivity and responsiveness of the PedsQL 4.0 Generic Core Scales. The population included pediatric patients (age range two to 18 years) with acute or chronic health conditions (n = 115 presenting to a cardiology clinic; n = 47 presenting to an orthopedic clinic; n = 127 presenting to a rheumatology clinic) and their parents. Statistically significant differences were observed between pediatric patients defined as Class II/IV New York Health Assessment (NYHA) and Classes I and II NYHA, suggesting that the PedsQL was likely to be sensitive.[31] Likewise, statistically significant changes between the initial and follow-up visit of patients attending the orthopedic clinic were observed (and the follow-up visit results also corresponded to that of healthy children responses), demonstrating the responsiveness of the PedsQL.[31] In another study by Desai et al.,[41] patients admitted to medical or surgical units were administered the PedsQL 4.0 upon admission (64.5%; n = 4637/7184) and during follow-up (58.1%; n = 2694/4637). The responsiveness of the PedsQL was demonstrated upon examination of the mean differences between admission and follow-up: 22.1 (standard deviation [SD] of 22.7) for the total score; 29.3 (SD of 32.4) for the physical domain; and 17.1 (SD of 21.0) for the psychosocial domain. Moderate variability in responsiveness was observed by age and minimal variability in responsiveness was observed for patients having been admitted for medical or surgical reasons.[41] Construct validity was further demonstrated as patients with no chronic illness (and their parents) scored higher on the total score, physical domain, and psychosocial domain when compared with patients with either complex or non-complex chronic illness.[41]

In a large study by Varni et al.[32], the authors mailed out a survey to residents in California (of which 10,241 [51%] completed and returned the survey) in the hopes to further examine the validity, reliability, and feasibility of the PedsQL 4.0 Generic Core Scales. In this study, the authors also explored the MCID by calculating the Standard Error of Measurement in the survey responses. The authors noted that in previous studies the Standard Error of Measurement has been shown to be linked to the MCID, with the two having excellent agreement. They determined the MCID for the Total Scale Score of the child self-report is a change of 4.4, while the MCID for the Total Scale Score for parent proxy-report is a change of 4.5.[32] No MCID, however, was identified for patients with LAL-D.

Conclusion

- The CLDQ has been shown to be valid, reliable, and responsive in patients suffering from CLD. There is some evidence to suggest that a change of 0.5 on the scale from 1 to 7 would signify an important difference in score in patients suffering from CLD; however, there is no indication that this was validated using conventional methods for estimating a MCID. No MCID was identified specifically for patients with LAL-D.
- The FACT was validated in cancer patients; however, there is no evidence that the FACIT-F has been validated in patients with LAL-D. In addition, no information was identified regarding the MCID of FACIT-F in patients with LAL-D; however, the MCID in the FACIT-F ranged from 3 to 4 points in patients with rheumatoid arthritis.
- The PedsQL 4.0 Generic Core Scales have been validated and determined to be reliable and responsive in pediatric patients with chronic conditions. The MCID for the Total Scale Score of the child self-report is a change of 4.4, while the MCID for the Total Scale Score for parent proxy-report is a change of 4.5 (assessed in patients with a variety of chronic conditions). However, no MCID was identified in patients with LAL-D.

Appendix 6: Summary of ARISE Extension Study

Objective

To summarize the efficacy and safety results of the ARISE extension study. The following summary is based on published data.[16] [redacted].

Trial Description

Patients from the original double-blind portion of the ARISE trial were permitted to continue into the open-label (OL) extension phase of the trial. All patients were treated with 1 mg/kg sebelipase alfa in the OL extension phase (starting at week 22) regardless of whether they were in the sebelipase alfa or placebo arms earlier in the double-blind period. At the time of the interim report (cut-off 30 May 2014), data were available for patients who continued in the 1 mg/kg sebelipase alfa for up to 42 weeks; however, most data are provided up to week 36 (which is the last point at which more than five patients in each treatment group had data available).
A patient may have received a total of up to 64 infusions over this maximum 130-week OL period. The Investigator, in consultation with the Sponsor, may have considered increasing a patient's dose to 3 mg/kg every other week if the patient exhibited an inadequate clinical response after receiving at least eight consecutive OL every other week infusions of sebelipase alfa at a dose of 1 mg/kg every other week.

Results

Patient Disposition

Of the 36 patients that entered in the double-blind randomized period of ARISE, 35 (97%) of patients who received sebelipase alfa and 30 (100%) patients who received placebo in the double-blind randomized period of the ARISE trial entered the OL extension period, with all patients receiving 1 mg/kg sebelipase alfa every other week. At the time of the interim report, no patients had discontinued from the OL period and all were still continuing to receive sebelipase alfa.

Detailed patient disposition is presented in Table 23.

Table 23: Patient Disposition in the ARISE Trial through Week 36[a] of the Open-Label Extension Period

	ARISE	
	Sebelipase Alfa n (%)	**Placebo n (%)**
Patients randomized at ARISE baseline	36 (100)	30 (100)
Patients included in FAS[b]	36 (100)	30 (100)
Patients completing DB period	35 (97)	30 (100)
Patients continuing to OL period	35 (97)	30 (100)
Patients discontinuing study after DB period	0	0
Patients entering OL period	35 (97)	30 (100)
Patients discontinued from OL period	0	0
Patients completing OL period	0	0
Patients continuing in OL period	35 (97)	30 (100)

DB = double blind; FAS = full analysis set; OL = open-label.
[a] The last time points at which > 5 patients in each treatment group had data available.
[b] Defined as patients who received at least one study drug infusion.
Source: ARISE LAL-CL02-CSR.[22]

Drug exposure

When data from the OL period were considered, the maximum number of sebelipase alfa infusions received for an individual patient [redacted]

Detailed drug exposure data are presented in Table 24.

Table 24: Study Drug Exposure During Treatment with Sebelipase Alfa in the ARISE Trial (EAS[a])

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EAS = extension analysis set; PBO = placebo; SA = sebelipase alfa.
[a] Comprised of patients in the Consented Set who, in addition, were randomized to treatment and received at least one dose (or any portion of a dose) of sebelipase alfa. For patients who were originally randomized to sebelipase alfa and received at least one dose of sebelipase alfa (SA/SA), all assessments from both the double-blind and the open-label period were included in the EAS. This included patients who were dosed in the double-blind phase with SA, but did not initiate open-label SA. For patients who were originally randomized to placebo and received at least one dose of sebelipase alfa in the open-label period (PBO/SA), only assessments from the open-label period were included in the EAS.
Source: ARISE LAL-CL02-CSR.[22]

Efficacy Results

Clinical Outcomes

It appeared that there was a sustained effect of long-term SA treatment on ALT normalization, with [redacted] (Table 25).

[redacted] (Table 25).

[redacted] (Table 25).

[redacted] (Table 25).

Detailed efficacy data are presented in Table 25.

Table 25: ALT Normalization, AST Normalization, HDL-C Increase, LDL-C Reduction, Non-HDL-C Reduction, TG Reduction, Liver Fat Volume, Liver Volume, Weight Change, and Height Change in the ARISE OL Extension Period (EAS[a])

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; EAS = extension analysis set; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MN = multiples of normal; NR = not reported; OL = open-label; SA = sebelipase alfa; SD = standard deviation; TG = triglycerides.

[a] Extension analysis set. Comprised of patients in the Consented Set who, in addition, were randomized to treatment and received at least one dose (or any portion of a dose) of SA. For patients who were originally randomized to sebelipase alfa and received at least one dose of sebelipase alfa (SA/SA), all assessments from both the double-blind and the open-label period were included in the EAS. This included patients who were dosed in the double-blind phase with SA, but did not initiate open-label SA. For patients who were originally randomized to placebo and received at least one dose of sebelipase alfa in the open-label period (PBO/SA), only assessments from the open-label period were included in the EAS.

[b] A value of MN > 1.0 indicate an organ volume which is greater than the expected normal size.

Source: ARISE LAL-CL02-CSR[22] and Burton et al. 2015[16].

Patient-Reported Outcomes and Antibody Development Information

Patient-reported outcomes (PROs) were only available for patients who were 17 years or older at date of informed consent in both the double-blind and OL periods of the ARISE trial.

[redacted]

[redacted] (Table 26).

[redacted] (Table 26).

Details regarding the PROs and antibody development information are presented in Table 26.

Table 26: Patient-Reported Outcomes FACIT-F, CLDQ, and PedsQL in the ARISE OL Extension Period (EAS[a])

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ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLDQ = Chronic Liver Disease Questionnaire; EAS = extension analysis set; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; OL = open-label; PBO = placebo; PedsQL = Pediatric Quality of Life Inventory; SA = sebelipase alfa; SD = standard deviation.
Note: Week 32 was the only week available.
[a] Comprised of patients in the Consented Set who, in addition, were randomized to treatment and received at least one dose (or any portion of a dose) of SA. For patients who were originally randomized to sebelipase alfa and received at least one dose of sebelipase alfa (SA/SA), all assessments from both the double-blind and the open-label period were included in the EAS. This included patients who were dosed in the double-blind phase with SA, but did not initiate open-label SA. For patients who were originally randomized to placebo and received at least one dose of sebelipase alfa in the open-label period (PBO/SA), only assessments from the open-label period were included in the EAS.
[b] FACIT-F total score only available for patients who are 17 years or older at date of informed consent. The total score ranges from 0 to 52; a higher value indicates a better quality of life.
[c] CLDQ questionnaire only available for patients who are 17 years or older at date of informed consent. Total score and single domains range from 0 to 7; higher values indicate a better quality of life.
[d] PedsQL questionnaire only available for patients who are 5 years to ≤ 18 years old at date of informed consent. Total score, summary scores, and single domains range from 0 to 100; higher values indicate a better quality of life.
Source: ARISE LAL-CL02-CSR.[22]

Safety Results

[redacted] (Table 27).

Detailed harms data are presented Table 27.

Table 27: Harms in the ARISE Trial (Extension Analysis Set)[a]

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AE = adverse event; EAS = extension analysis set; OL = open-label; PBO = placebo; SA = sebelipase alfa; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Comprised of patients in the Consented Set who, in addition, were randomized to treatment and received at least one dose (or any portion of a dose) of SA. For patients who were originally randomized to sebelipase alfa and received at least one dose of sebelipase alfa (SA/SA), all assessments from both the double-blind and the open-label period were included in the EAS. This included patients who were dosed in the double-blind phase with SA, but did not initiate open-label SA. For patients who were originally randomized to placebo and received at least one dose of sebelipase alfa in the open-label period (PBO/SA), only assessments from the open-label period were included in the EAS.

Source: ARISE LAL-CL02-CSR.[22]

Critical Appraisal

The main limitations inherent to the ARISE extension period was the open-label nature of the study, the lack of a proper control group, and the lack of power necessary to perform meaningful statistical analysis. The aforementioned precludes the ability of one to ascertain either a statistical or clinical significance between the SA and placebo groups. However, the main purpose of extension study is to provide some insight into the efficacy and safety associated with the treatment; therefore, it is appropriate to mention that there were no unexpected changes with the efficacy or safety in terms of the a priori outcomes.

Summary

No unexpected changes in efficacy or new safety signals were evident in the OL extension period of the ARISE trial. It appeared ALT and AST normalization were sustained at week 36, along with continual improvements in LDL-C, HDL-C, non-HDL-C, and triglycerides; however, the number of patients contributing to these outcomes were small. No new safety signals were apparent, with 96% of patients experiencing at least one adverse event (the most common of which were headache, diarrhea, and pyrexia) and 6% experiencing a serious adverse event. In addition, five patients (14%) were positive for antibodies in the extension analysis set. However, due to the limitations inherent to the ARISE extension period (open-label nature of the study, the lack of a proper control group, and the lack of power necessary to perform meaningful comparison with statistical analysis), no definitive conclusions can be made regarding the long-term treatment of SA 1mg/kg.

Appendix 7: Clinical Trials not Included in the Systematic Review — LAL-CL06

Background

The aim of this section is to summarize the phase II, single-arm, open-label study LAL-CL06 trial [redacted][7].

Trial Description

[redacted]

Study Participants

[redacted]

Efficacy results

[redacted]

[redacted]

Safety Results

[redacted]

Critical Appraisal

[redacted]

Summary

[redacted]

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